Chemical and electrochemical coupling of heterocyclic substrates.

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CHEMICAL AND ELECTROCHEMICAL COUPLING OF HETEROCYCLIC SUBSTRATES

submitted by MARK POWELL

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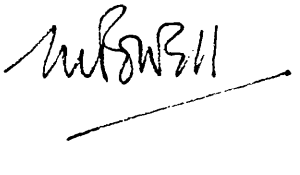

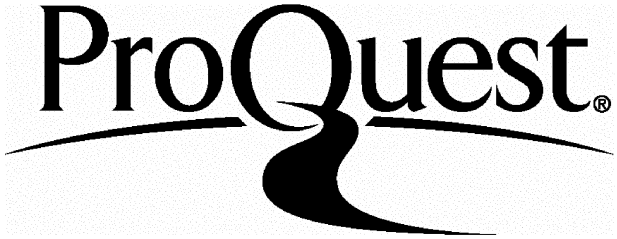

I N T R O I B O A D A L T A R E D E I

A D M A J O R E M D E I G L O R I A M

ACKNOWLEDGEMENTS

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SUMMARY

A study has been made of the chemical and electrochemical oxidations of certain substituted indoles and isoquinolines.

A great deal of time was devoted to the synthesis of 2-(3,4-dimethoxyphenylpropanoyl)indole for electrochemical investigation in an attempt to determine the true structure of the oxidation product from the corresponding 3-substituted indole.

A variety of acylated indoles were synthesised for oxidation reactions using palladium (II) acetate and successful coupling reactions were carried out on two 3-benzoylindole derivatives.

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline has been oxidised electrochemically to a tetracyclic structure whereas electrolysis of the hydrochloride salt of this base leads only to the 4-benzylidene derivative. The mechanistic consequences of this result are discussed. The 4-phenethyl homologue has been oxidised with thallium (III) trifluoroacetate and another intramolecular coupling resulted.

4-(3,4-Dimethoxyphenylacetyl)-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline was prepared and shown to be electrochemically inert. Finally, a search was made for a synthetic pathway to the corresponding 4-(3,4-dimethoxyphenylpropanoyl) compound.

INSTRUMENTAL METHODS

All i.r. spectra were determined on a Perkin-Elmer 197 spectrophotometer as nujol mulls or liquid films. U.v. spectra were determined on a Perkin-Elmer 402 spectrophotometer in 95% ethanol. ^{1}H n.m.r. spectra were recorded on a J.E.O.L. PS100 spectrometer. ^{13}C n.m.r. spectra were recorded on a J.E.O.L. FX90Q spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane as internal standard. Mass spectra were recorded on an A.E.I. MS12 spectrometer. Melting points are uncorrected. The elemental analyses were carried out by Dr. F.B. Strauss at Oxford.

Cyclic voltammograms were recorded using a Thompson DRG 16 ramp generator and precision potentiostat. Preparative electrolyses were carried out using a Farnell stabilised voltage supply.

CONTENTS

INTRODUCTION

Organic Electro-oxidative Chemistry

The electrochemical oxidation of organic molecules is a technique which finds its origins in the Kolbe synthesis of alkanes from carboxylate anions[1].

$$2\ RCOO^- \xrightarrow{-2e^-} 2\ RCOO^\bullet \longrightarrow 2\ R^\bullet \downarrow R\text{-}R \quad + \quad 2\ CO_2$$

Until comparatively recently there has been little interest in the subject apart from studies of the Kolbe reaction. The main reason for this has been the difficulty experienced in interpreting complex electrode processes. The development of cyclic voltammetry has largely overcome this problem by aiding the elucidation of the reaction mechanisms.

All chemical reactions involve electron transfer so controlled potential electron exchange at an electrode offers a distinct advantage over the use of chemical reagents which only approximate to the redox potentials of the desired reactions.

Radical cations formed by anodic removal of electrons from organic molecules are generally highly reactive and react rapidly in secondary chemical processes to form more stable derivatives. The electrode process is therefore essentially irreversible. This means that classical theories (e.g. the Nernst equation) based on electrode process reversibility cannot successfully be applied.

Organic electrochemistry is a very broad subject and only a limited aspect of it is studied here, namely the anodic oxidation of selected aromatic and heteroaromatic substrates leading to intramolecular coupling reactions.

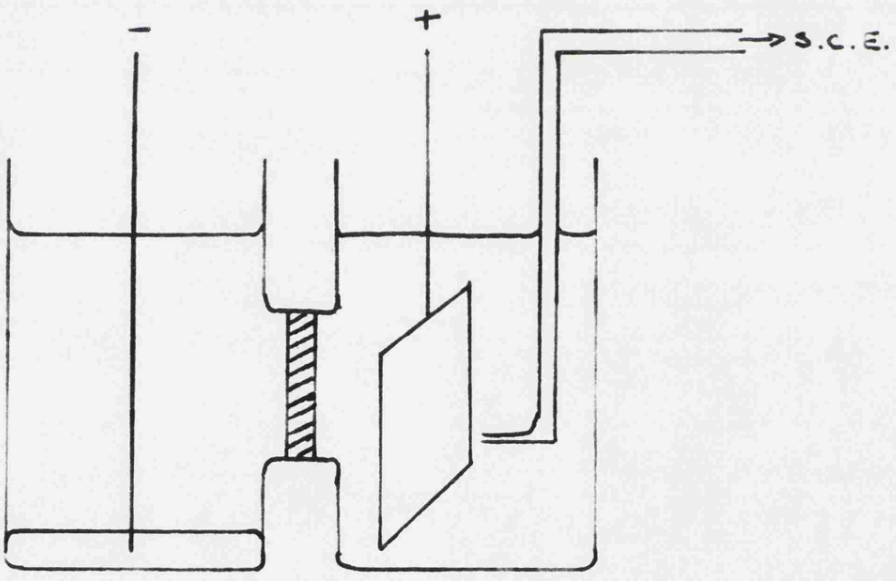
The Electrochemical Cell

The design of the vessel in which an electrochemical reaction is to be carried out depends primarily on the nature of the reaction.

Basically, the cell consists of an anode and a cathode immersed in an electrolyte. The electrolyte is a conducting solution usually consisting of a solute (the supporting electrolyte) in a solvent. On applying a potential difference across the electrodes current flows through the cell and electrolysis occurs.

For all reactions studied here a simple two-compartment cell such as the "H-cell" (figure 1) was used.

Figure 1



The anode is contained in one compartment and the cathode in the other. The compartments are divided by a porous glass frit which permits ionic conductance but inhibits diffusion of the substrate from the anodic compartment.

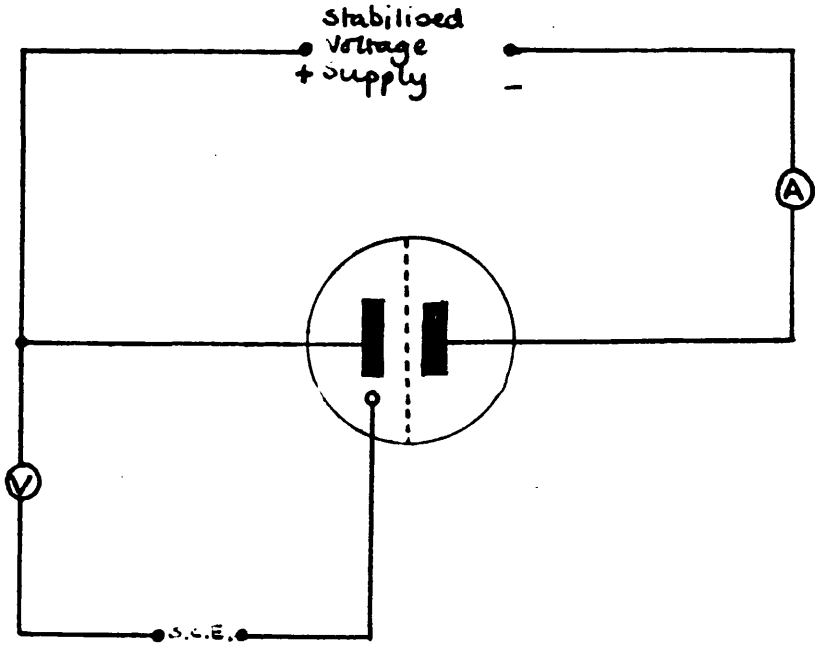
The nature of the cathode material is not critical and generally either a mercury pool or a platinum gauze are used. On the other hand, there are rather more limitations on the nature of the anode material due to the fact that most metals are themselves oxidised at low electrode potentials. The materials most commonly used are platinum gauze and carbon felt[2].

The standard calomel electrode[3] (SCE) is used as a reference electrode to measure the potential difference between the anode surface and the solution adjacent to it. The SCE consists of mercury in contact with mercurous chloride (calomel) in contact with molar potassium chloride solution. This gives rise to a potential of 0.28 volts measured against the standard hydrogen electrode.

$$\tfrac{1}{2}\ HgCl_2 + e \rightleftharpoons \tfrac{1}{2}\ Hg + Cl^-$$

The SCE is connected to the electrolyte *via* a conducting salt bridge (potassium chloride in agar[4]). This is important because mercurous chloride is unstable in the presence of some organic solvents (e g. acetonitrile).

Figure 2



An external voltage is supplied to the cell (figure 2) to maintain a practical rate of electrolysis. The magnitude of this will depend on the electrical resistivity of the electrolyte and the cell. For minimum resistance the distance between the anode and the cathode should be as small as possible.

The Electrolyte

Most organic compounds are insoluble in water, and water is reactive towards cations and cation radicals which are the intermediates in anodic reactions. Thus the electrolyte system is preferably based on organic solvents. The ideal solvent must fulfil several requirements.

1. It must be electrochemically inert in the potential range of the reaction.
2. It must be a good solvent for organic substrates.
3. It must be unreactive towards the intermediates present in the electrochemical reaction.
4. It must have a fairly high dielectric constant in order to minimise the electrical resistance of the electrolyte.
5. It must be relatively easily purified and dried.

In view of these criteria, acetonitrile is probably the best solvent for electrochemical oxidations and is certainly the most widely used.

The restrictions on the supporting electrolyte are similar to those for the solvent and, obviously, solubility in the solvent is another important factor. The salts most commonly used are alkali metal perchlorates and tetra-n-alkyl ammonium tetrafluoroborates[5].

For the oxidations described in this thesis the electrolyte used was a 0.1 molar solution of sodium perchlorate in dry acetonitrile. This system is stable to oxidation below + 2.0 volts[6].

Some Basic Electrochemical Laws

In 1834 Faraday[7] proposed two basic laws relating the quantity of electrical charge consumed in an electrolysis to the amount of material used:

1. The amount of material transformed is proportional to the quantity of charge passed (Q).
2. The masses of the various materials transformed (W) are proportional to their respective molecular weights (M).

$$W = \frac{MQ}{96{,}495n}$$

The number 96,495 is the "Faraday". It is the number of coulombs of charge necessary to transform one molecular equivalent of substrate in a one electron reaction. The letter "n" represents the number of electrons transferred per molecule.

However, due to losses in energy such as convected heat, solvation effects and the energies of undesirable side reactions, electrochemical reactions are never 100% efficient. Thus the consumption of one Faraday of charge per molecular equivalent rarely results in the formation of one equivalent of product.

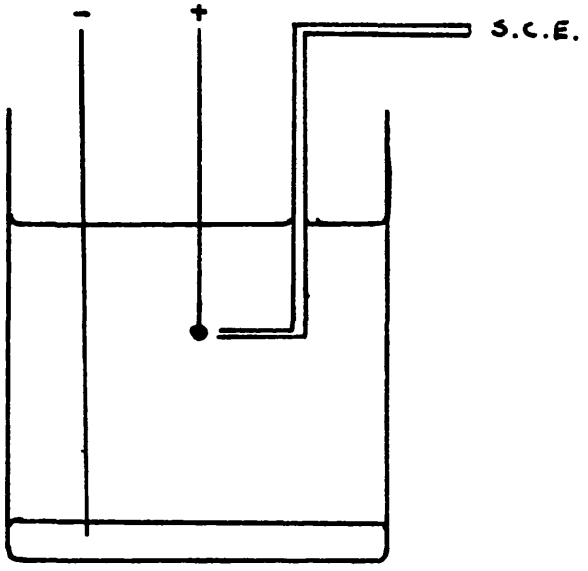
Cyclic Voltammetry

Classical polarography, introduced in 1922 by Heyrovsky[8], has largely been superseded by other electroanalytical techniques. The most important of these new techniques is cyclic voltammetry.

Voltammetry is able to provide approximate data on the potentials at which to conduct preparative electrolyses and also enables an analysis of the probable events occurring after the initial ionisation step.

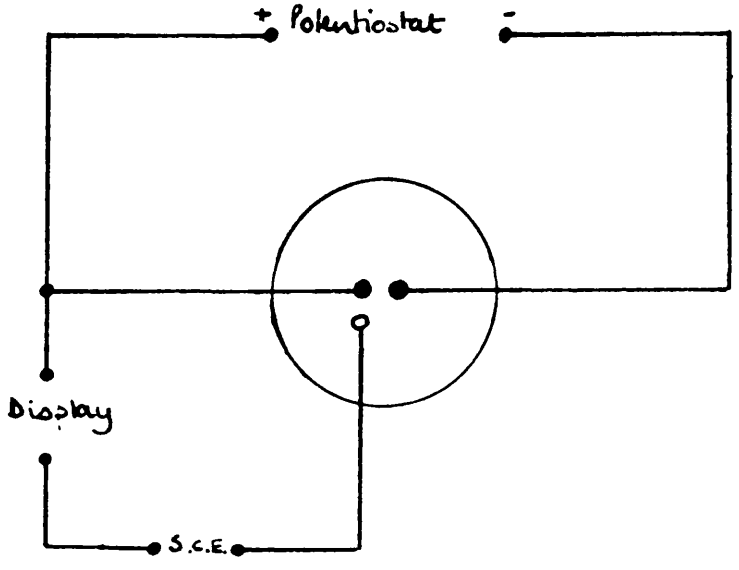
The electrodes used in voltammetry can be the same as used in preparative electrolyses. Platinum bead microelectrodes are the most widely used, in conjunction with a simple one-compartment cell (figure 3).

Figure 3



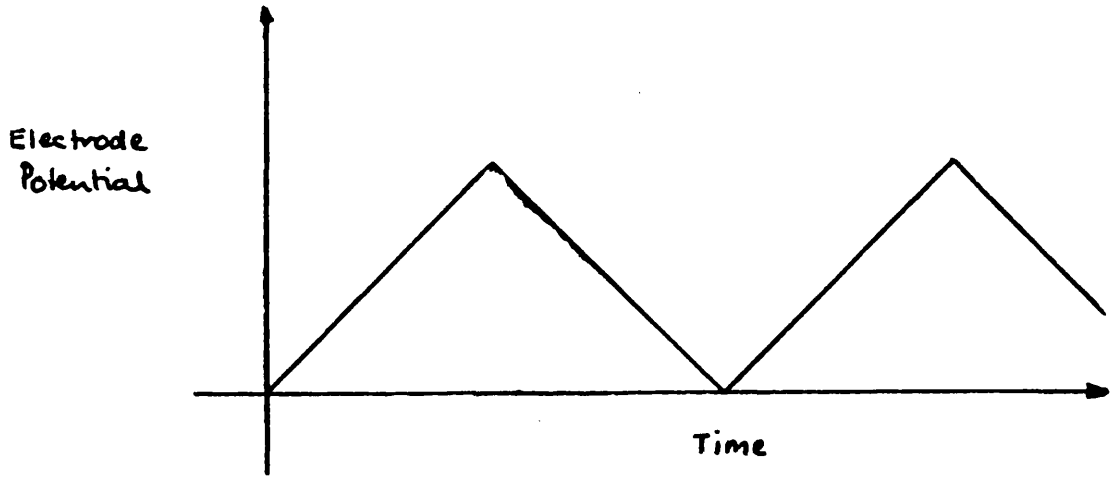
In cyclic voltammetry the electrode potential is linearly swept whilst the current through the working electrode is monitored (figure 4).

Figure 4



A "sawtooth" waveform (figure 5) is applied to the working electrode and is represented as the "X" ordinate on an oscilloscope or "X-Y" plotter. The current change is measured as the change in potential difference across a "counting" resistor and is displayed as the "Y" ordinate on the recording device.

Figure 5



Due to the secondary chemical processes which normally occur in organic electrode reactions the first and second sweeps are often quite different and steady state conditions are normally reached after five to ten cycles.

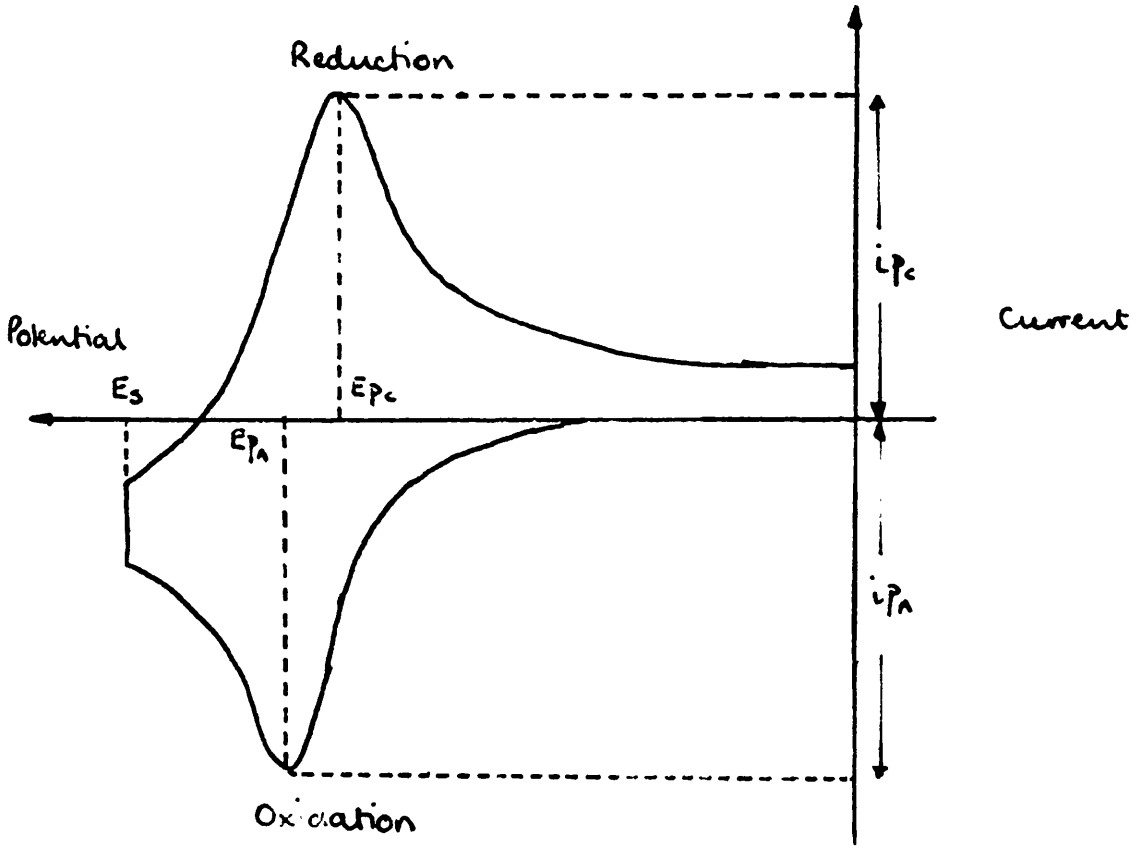
The first case to be considered is that of a reversible one electron process. As the electrode potential increases current begins to flow in the cell as the electroactive substrate (S) is oxidised.

$$S \rightleftharpoons S^{+} + e$$

The current rises rapidly until all the electroactive material around

the electrode is consumed and the supply of substrate by diffusion from the bulk phase is exceeded. At this point the current falls giving rise to a point of inflexion in the voltammogram (Ep_A, figure 6) as the concentration of substrate around the electrode is zero. The maximum current (ip_A) is proportional to the peak height.

Figure 6



The peak potential (Ep) of a reversible oxidation is independent of scan speed[9], but this is not true of an irreversible process[10]. This can be a useful criterion in determining reversibility.

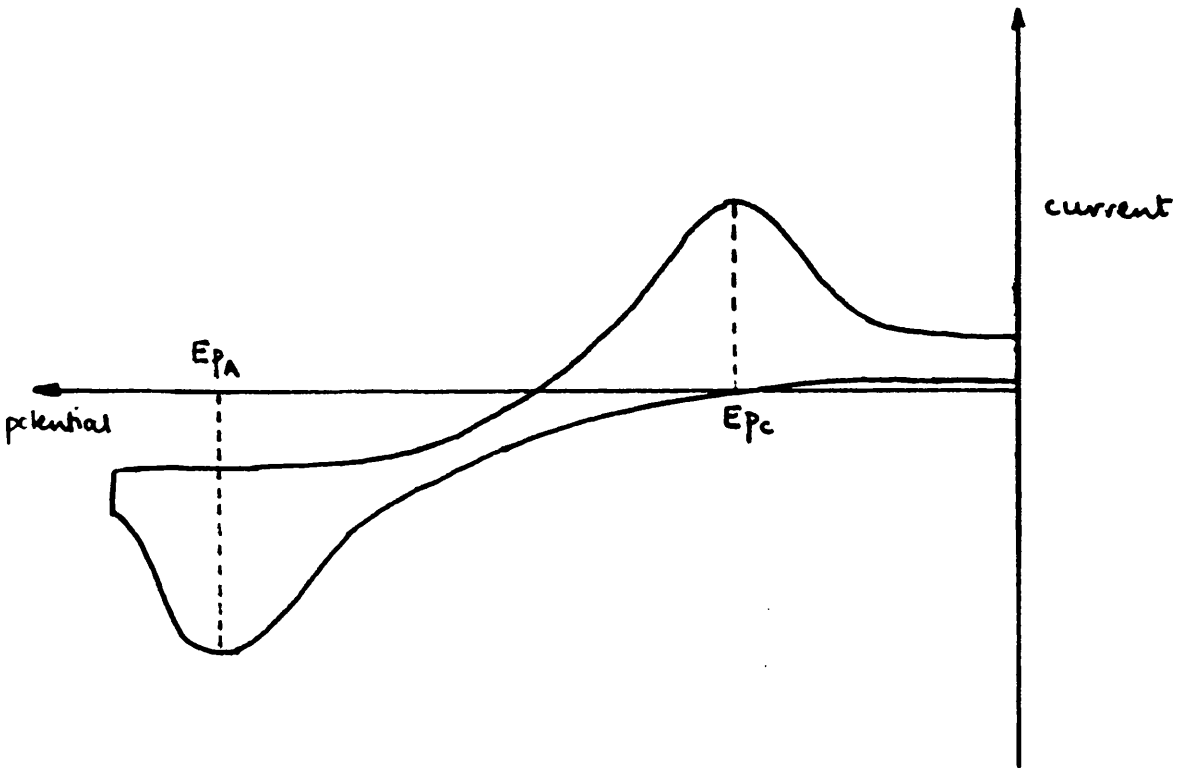
At a predetermined value (Es, the switching potential) the voltage

sweep is reversed and current flows in the opposite direction. At this point the electrode is surrounded by oxidised species which are then reduced at the appropriate potential (Ep_c) giving rise to a reduction peak.

For a truly reversible reaction the ratio of peak currents (ip_c/ip_A) will be unity.

In the second case of an irreversible oxidation which proceeds without an accompanying chemical reaction the peaks will be broader at higher scan speeds and oxidative peaks will become progressively more anodic on increasing the scan speed. Reductive peaks will be displaced equally, but in a cathodic direction (figure 7).

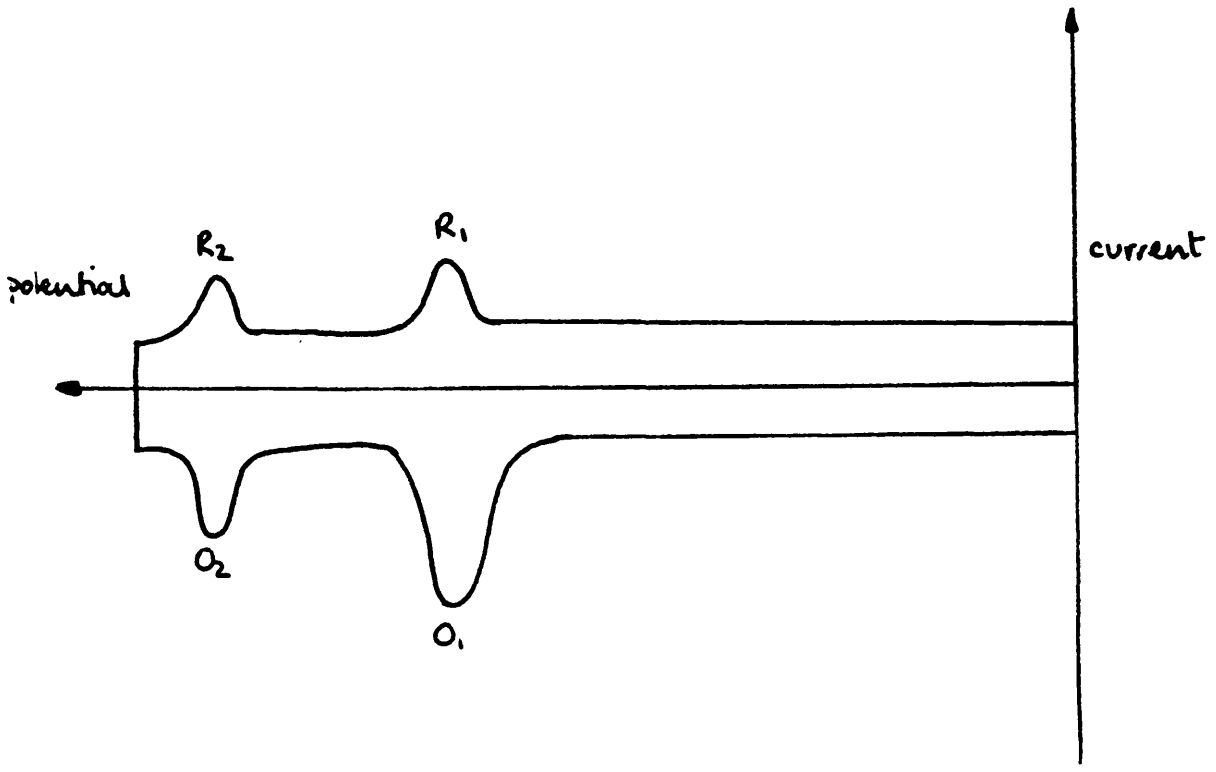
Figure 7



The distinction made here between reversible and irreversible electrode processes is purely artificial and is only based on the rates of charge transfer which can be effected by the electrolyte and the electrode material.

For the third case of a reversible process with an associated chemical reaction (figure 8) the compound is oxidised at a potential O_1 to produce an oxidised species which is sufficiently reactive to form a product which is oxidised at the higher potential O_2. If complete conversion of the substrate has not been effected by the time the voltage sweep has recycled then the residual oxidised species will be reduced and a reductive peak R_1 will be observed. R_1 will not be seen if the oxidised species undergoes a fast chemical reaction compared to the

Figure 8



time scale of the sweep. R_1 will always be less intense than O_1. On the second and subsequent cycles O_1 will be reduced in intensity. R_2 may be observed due to the reduction of the species formed by the second oxidation O_2.

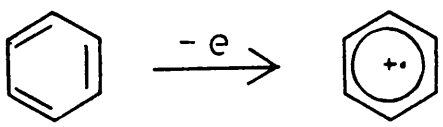
In this example two assumptions have been made. It was assumed that the chemical product has a higher oxidation potential than the substrate and that it forms a stable redox couple (O_2-R_2). In practice, however, the product is often oxidised below the oxidation potential of the starting material and on oxidation undergoes further chemical reactions. Overoxidation is one of the main factors responsible for low yields in some coupling reactions[11].

A quantitative assessment of the number of electrons involved in a mechanistic sequence can be made by integrating the voltammogram electronically and comparing the integral with that of an equimolar solution of 1,4-dimethoxybenzene which is oxidised in a one electron process at a potential of 1.34 volts.

Factors Affecting Oxidation Potentials

The primary electrochemical process in all the oxidation reactions presented in this thesis is the removal of electrons from an aryl nucleus.

Electron-donating substituents in the aryl nucleus will reduce the first oxidation potential of the substrate and stabilise the resultant cation radical (table 1).



Electron-withdrawing groups will have the reverse effect.

Table 1

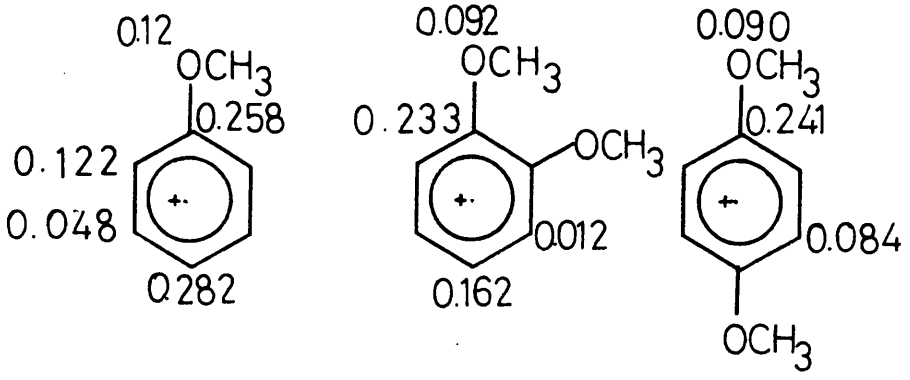
Oxidation potentials ($E_{\frac{1}{2}}$) in acetonitrile measured relative to the SCE.

Compound	$E_{\frac{1}{2}}$ (volts)
Benzene	2.39
Toluene	2.29
Biphenyl	1.91
Mesitylene	1.90
Thioanisole	1.82
Anisole	1.67
Hexamethylbenzene	1.52
Phenol	1.35
1,4-Dimethoxybenzene	1.34
1,2,4,5-Tetramethoxybenzene	0.81

Electron removal occurs from the highest occupied molecular orbital (HOMO)[12], and the presence of electron-donating substituents has the effect of raising the energy of this orbital[13] thus reducing the oxidation potential. The reactivity of the radical cation then formed depends to a large extent on the positions of substitution; thus the reactivity of the 1,2-dimethoxybenzene radical is greater than that of the 1,4-isomer. The latter forms a stable redox couple[14] whereas in the former case intermolecular coupling occurs at the *para* positions which have relatively high electron densities (figure 9) and are sterically unhindered[15]. Generally speaking *para* coupling is strongly favoured and *ortho* coupling is only observed when the *para* positions are blocked.

Figure 9

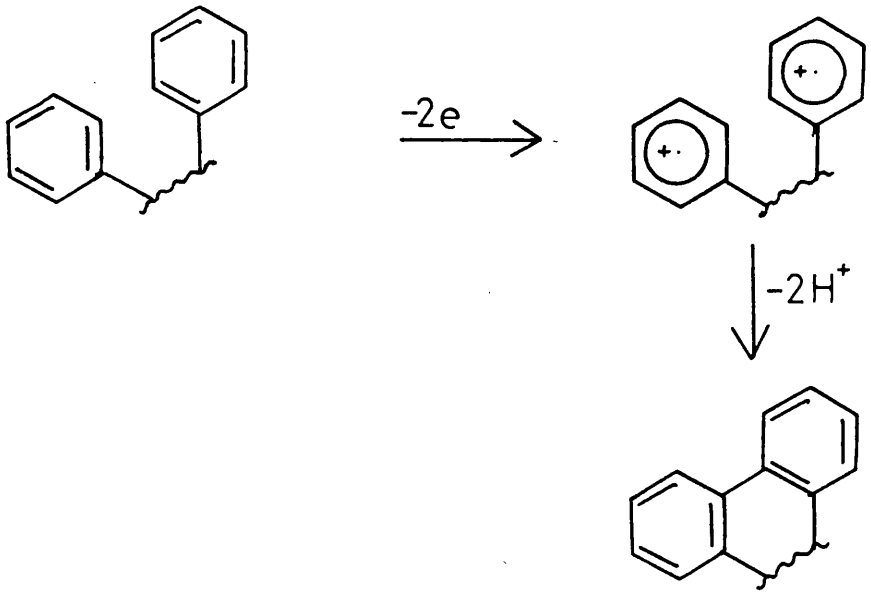
Electron spin densities in methoxybenzenes.



The Mechanism of Oxidative Coupling

Three mechanisms have been proposed for aryl-aryl coupling reactions. Parker[11] has proposed the "eec" reaction (scheme 1). This involves the

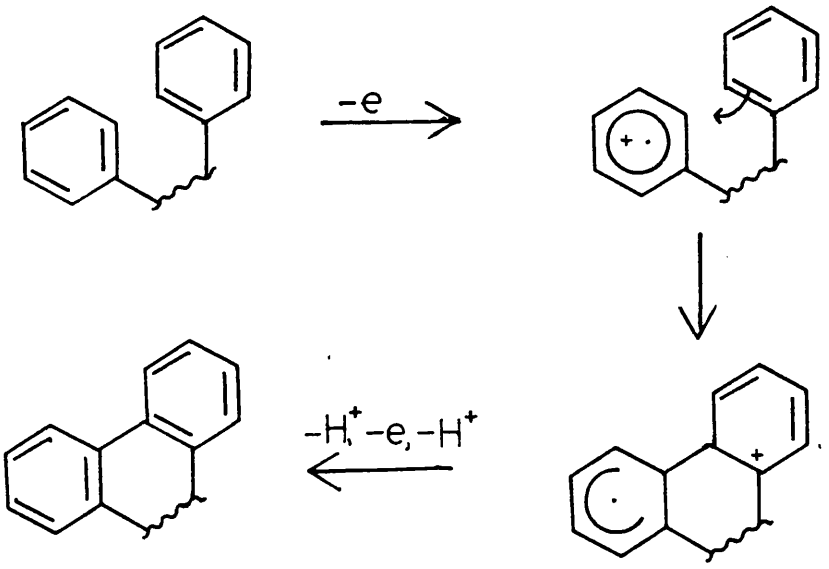
Scheme 1



loss of two electrons, one from each of the aryl rings, followed by a chemical reaction. The approach of two positively charged aryl nuclei seems unlikely at first sight but this type of reaction is assumed to be quite common in the literature[11]. When the two aryl nuclei have similar oxidation potentials this is the major reaction pathway.

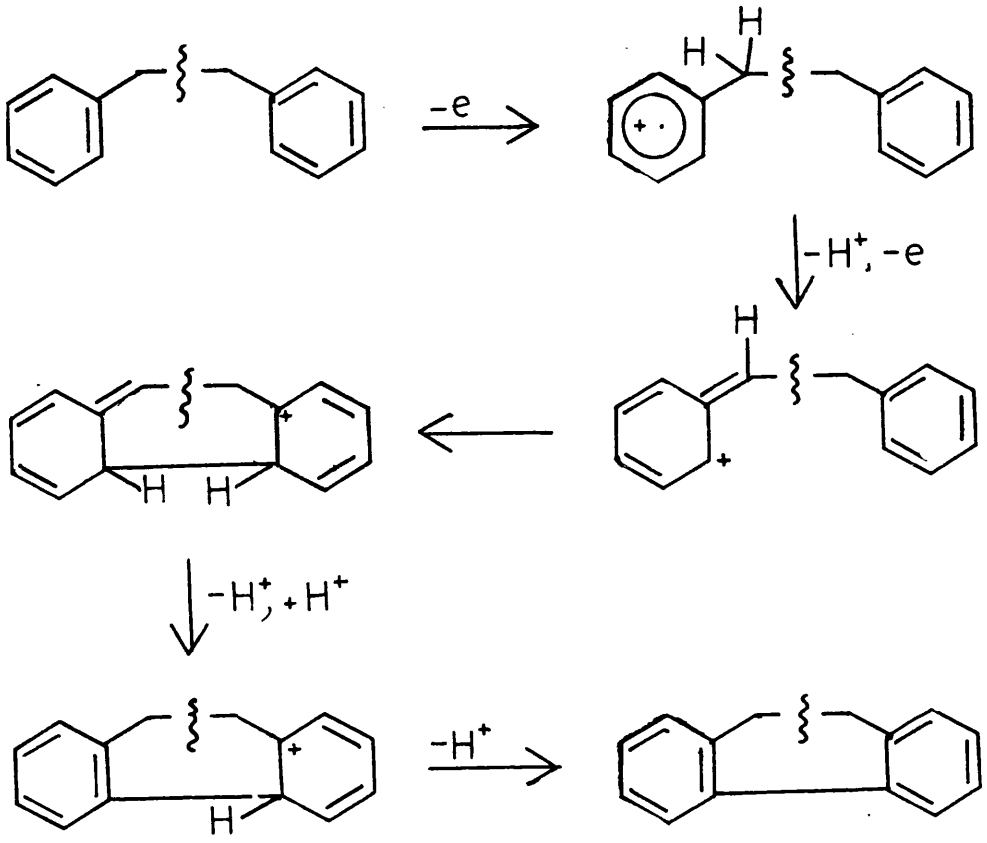
The "ece" reaction (scheme 2) has been advanced by Nyberg[16]. One of the aryl rings is oxidised and coupling then occurs with a non-ionised molecule. This is then followed by loss of a second electron and a proton; the nett result is, of course, the same.

Scheme 2



The third route has been proposed by Sainsbury and involves stabilisation of the intermediate as a benzylic cation (scheme 3).

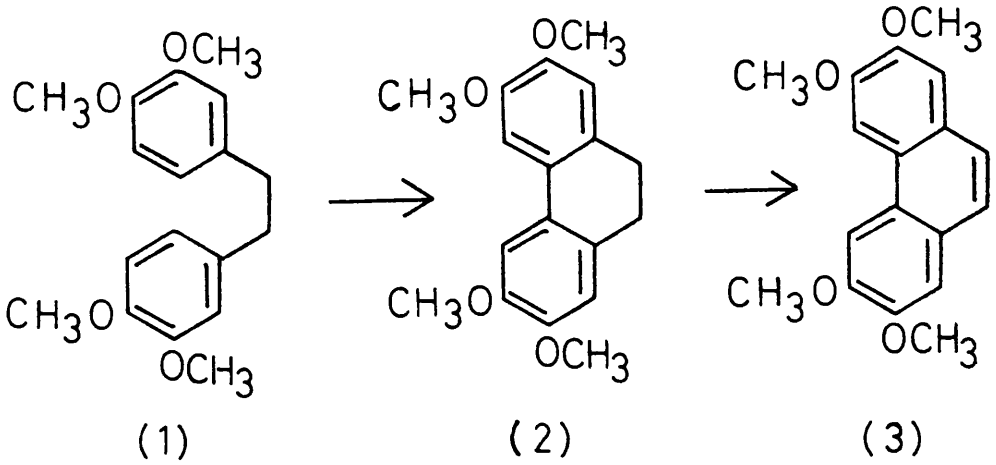
Scheme 3



An understanding of the "correct" mechanism is important since there are a number of anomalous results in the literature of reactions which should proceed but do not and in the beginning of this thesis some time was directed towards the investigation of the coupling reaction of a symmetrically substituted diarylethane.

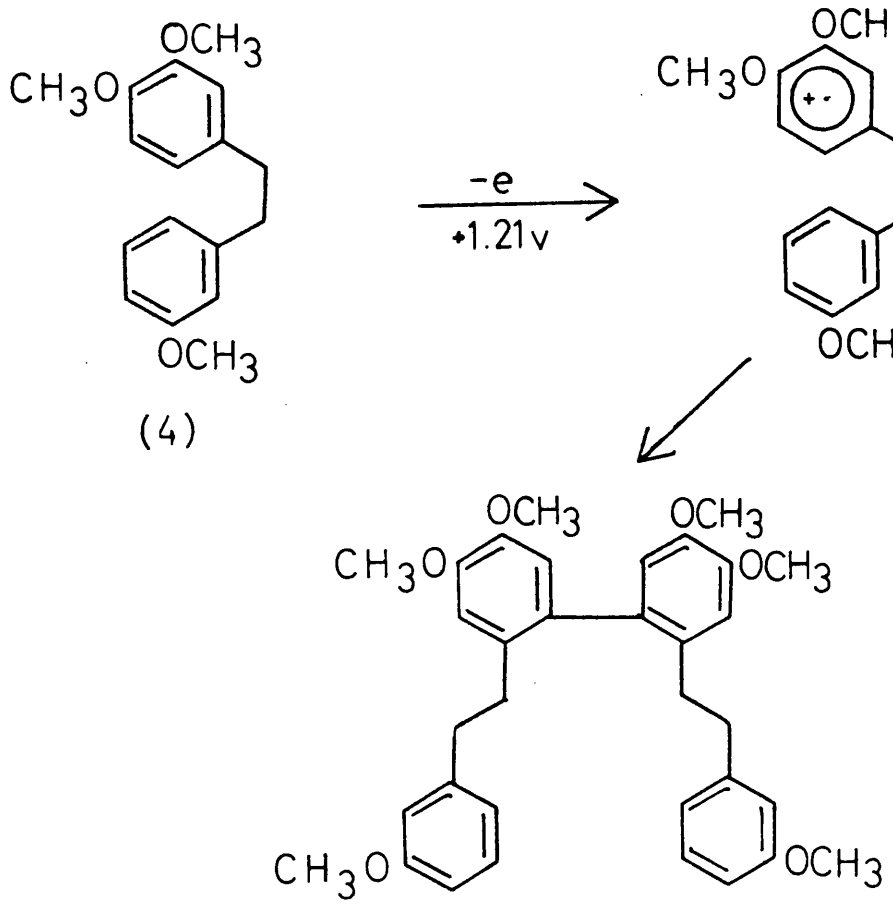
Some Simple Intramolecular Anodic Coupling Reactions

A great deal of work has been carried out on the electrochemical oxidation of diarylalkanes. Anodic oxidation of 3,3',4,4'-tetramethoxybibenzyl (1) gave the dihydrophenanthrene (2) which was further oxidised to the phenanthrene (3)[17].



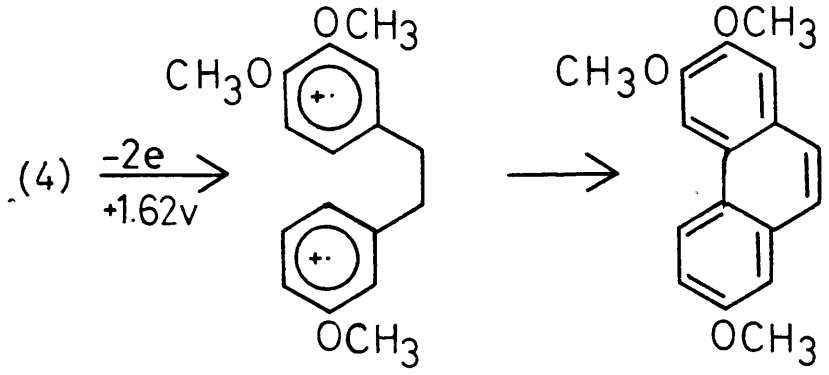
(1) (2) (3)

Oxidation[18] of the unsymmetrical 3,3',4-trimethoxybibenzyl (4) at + 1.21 volts gave rise to the dehydrodimer (5) by oxidation of the dimethoxy ring in an "ece" mechanism.



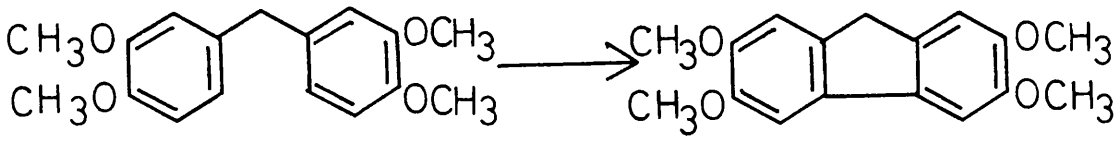
(4) (5)

However, oxidation at + 1.62 volts gave the diradical dic ation (6) by oxidation of both rings; this led to intramolecular coupling followed by dehydrogenation to give the phenanthrene (7). This is an example of the "eec" mechanism.

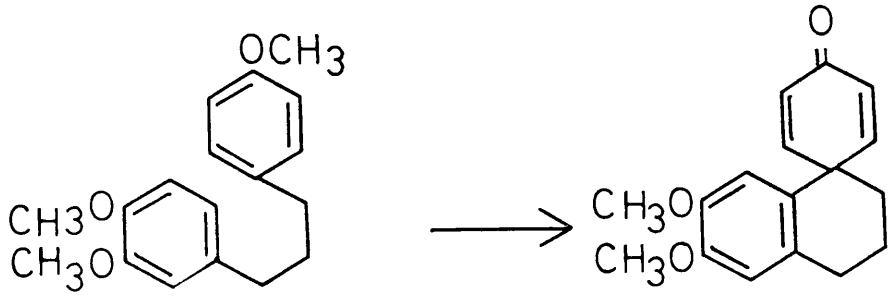


(6) (7)

Similarly, 3,3',4,4'-tetramethoxydiphenylmethane (8) on anodic oxidation gave the bridged biphenyl (9)[19]. Oxidation of the diarylpropane (10) gave the spirodienone (11)[20].



(8) (9)

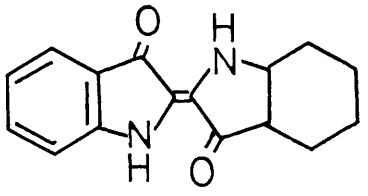


(10) (11)

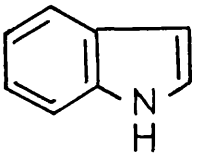
In this thesis the anodic oxidation of selected indoles and isoquinolines has been studied. A brief review of the synthetic routes to these heterocycles and their electrochemical reactions now follows.

Synthetic Routes to Acylated Indoles

The development of indole chemistry began with research on the natural dye indigotin (12) in 1841[21] for it was soon recognised that indoxyl, the simple oxidised derivative of indole, was the basic unit upon which the dye is constructed. The structure of indole (13) was proposed by Baeyer in 1869[22].

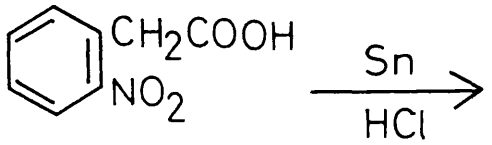


(12)



(13)

Similarly Baeyer also developed the first synthesis of an indole derivative by the reductive cyclisation of 2-nitrophenylacetic acid (14) to oxindole (15)[23].



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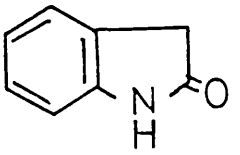
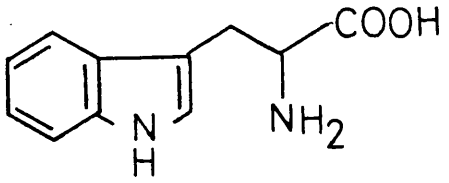


(15)

A revival of interest in indole derivatives came at the beginning of this century with the discovery of the indole alkaloids and other important compounds such as the essential amino acid tryptophan (16)[24] and the plant growth hormone heteroauxin (17)[25].



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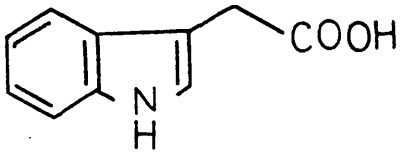
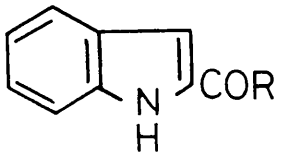


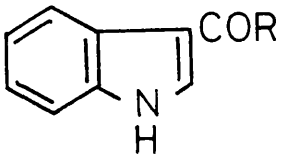
(17)

Since then indoles have continued to increase in significance in medicinal chemistry.

In this thesis a number of 2-acyl (18) and 3-acylindoles (19) were synthesised for subsequent electrochemical investigation and a short review of routes to these structures now follows.



(18)



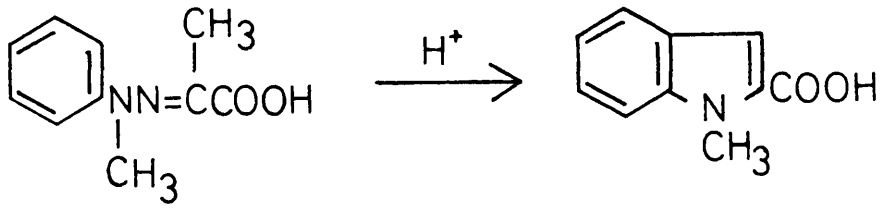
(19)

Two possibilities exist for the synthesis of acylated indoles. Either an indole precursor can be acylated before the indole ring system is formed or else an indole nucleus can be acylated.

Synthesis from Indole Precursors

The Fischer Indole Synthesis

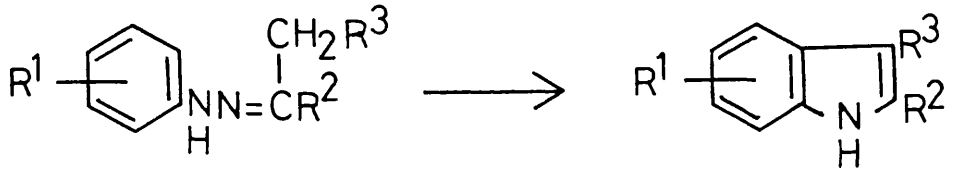
The classical method for preparing indoles is the Fischer synthesis[26]. 1-Methylindole-2-carboxylic acid (21) was prepared by heating the methylphenylhydrazone of pyruvic acid (20) in dilute hydrochloric acid.



(20) (21)

It was later found that yields were increased using zinc chloride as catalyst[27].

Since then the arylhydrazones of many carbonyl compounds (22) have been converted to indoles (23) with a variety of acids and metal halides.

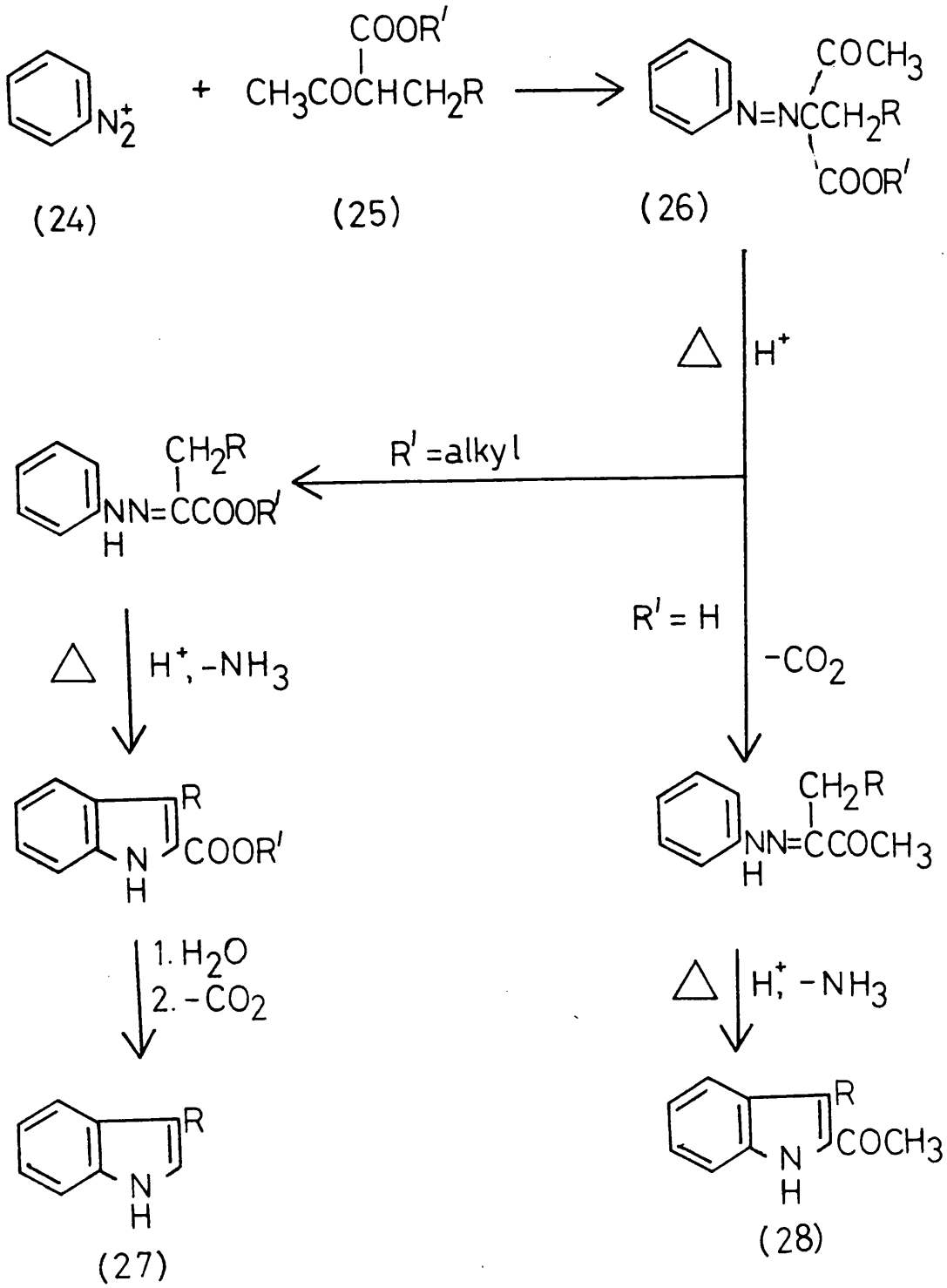


(22) (23)

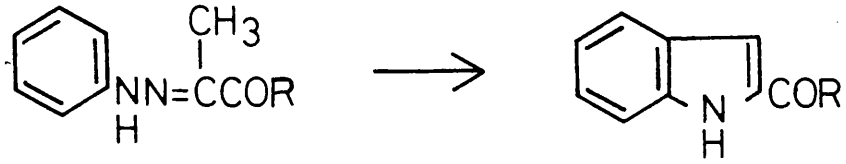
The mechanism proposed by Robinson and Robinson[28] assumed that an acid catalyst is required. However, it has been found that thermal indolisation[29] is also possible by heating in high boiling solvents such as ethylene glycol, diethylene glycol, or tetralin[30]. The acid catalysts most generally used are zinc chloride, sulphuric, hydrochloric, phosphoric, formic and acetic acids, boron trifluoride, polyphosphoric acid and polyphosphoric ester[31].

The most convenient method for preparing the required arylhydrazones is the Japp-Klingemann reaction[32] (scheme 4).

Scheme 4


COOR'
CH3COCHCH2R
COCH3
N=NCCH2R
COOR'
(24)
(25)
(26)
H+
R' =alkyl
CH2R
NN=CCOOR'
H
R' = H
-CO2
H+, -NH3
R
COOR'
CH2R
NN=CCOCH3
1. H2O
2. -CO2
H+, -NH3
R
COCH3
(27)
(28)

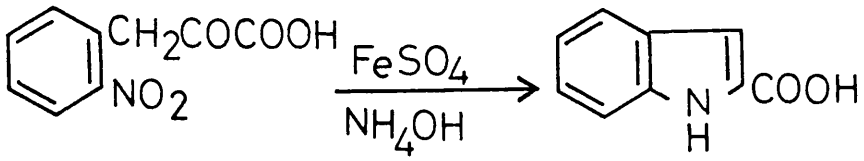
The reaction of a diazonium salt (24) with the substituted acetoacetic ester or acid (25) gives rise to the hydrazone (26) which is then cyclised to the corresponding indole (27 or 28). This synthesis can be applied to 2-acylindoles (29).



(29)

The Reissert Synthesis

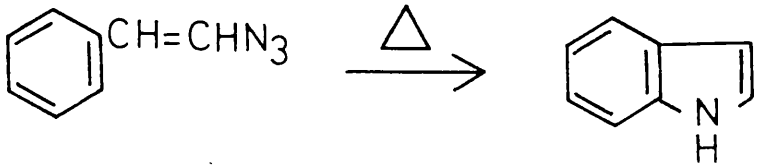
Indole-2-carboxylic acid (31) can be synthesised by the cyclisation of *o*-nitrophenylpyruvic acid (30)[33]. This reaction is of most use when the phenyl ring is substituted.



(30) (31)

Pyrolysis of Styryl Azides

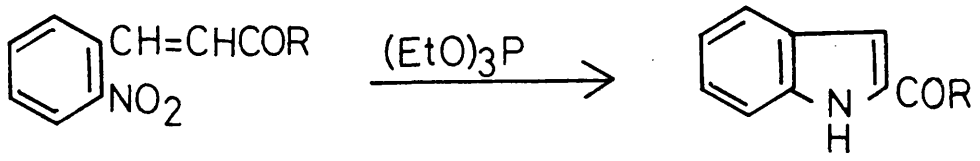
Indoles can be formed by the thermal cyclisation of styryl azides (32)[34].



(32)

Reduction of Nitrostyryl Ketones

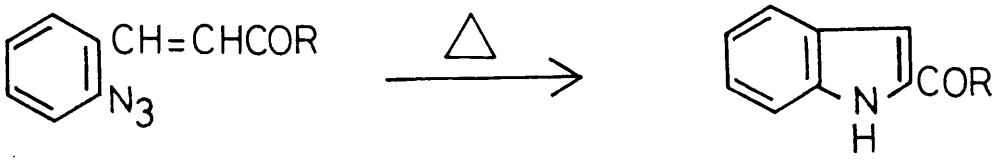
A useful route to 2-acylindoles is the triethyl phosphite reductive cyclisation of *o*-nitrostyrylketones (33)[35].



(33)

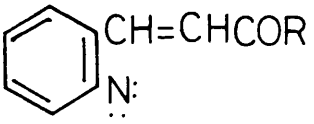
Pyrolysis of Azidostyryl Ketones

Thermal cyclisation of *o*-azidostyryl ketones (34) gives rise to 2-acylindoles[36].



(34)

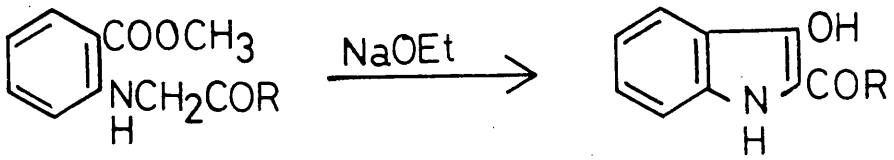
The mechanism in the last two reactions is essentially the same, that is, the generation of the nitrene (35) by thermal decomposition of an azide or the reduction of a nitro compound.



(35)

Cyclisation of Keto Esters

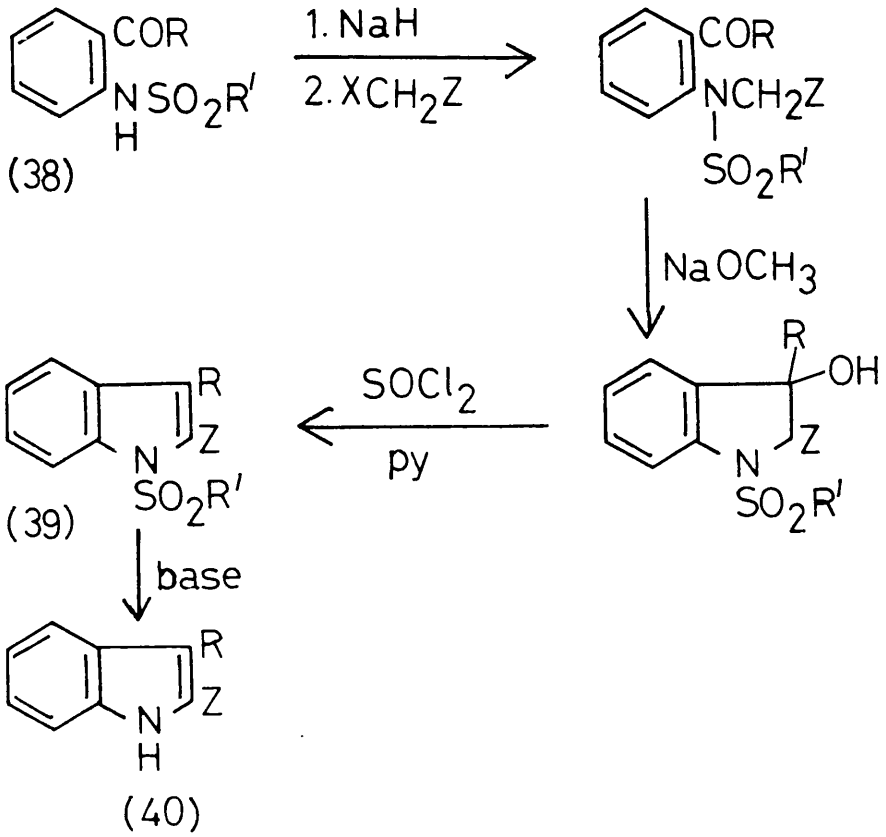
Base catalysed cyclisation of compounds of type (36) gives rise to 3-hydroxy-2-acylindoles (37).



(36) (37)

Cyclisation of Sulphonamides

The sulphonamides of *o*-aminocarbonyl compounds (38) are N-alkylated and then undergo base catalysed aldol condensation and subsequent dehydration to give 2-substituted indole sulphonamides (39). On hydrolysis the sulphonamides give rise to the corresponding indoles (40). This route is applicable to 2-acyl and 2-cyanoindoles[37].

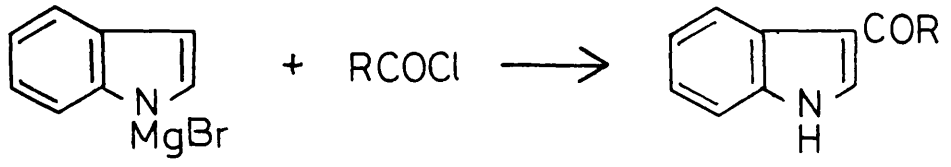


(38) (39) (40)

Synthesis from Indoles

Direct acetylation of indole with acetic anhydride gives a mixture of 1-acetyl- and 1,3-diacetylindole[38]. 1-Acetylindole is easily removed by steam distillation. The diacetylindole can be hydrolysed with sodium hydroxide to 3-acetylindole. For more complex acylindoles this route is of little synthetic utility. In general, acylation of indole with acid chlorides or anhydrides yields bis- and tris-indolyl systems[39].

The best route to 3-acylindoles is treatment of indole magnesium bromide (41) with an acid chloride[40]. This method was used to make all the 3-acylindoles included in this thesis.

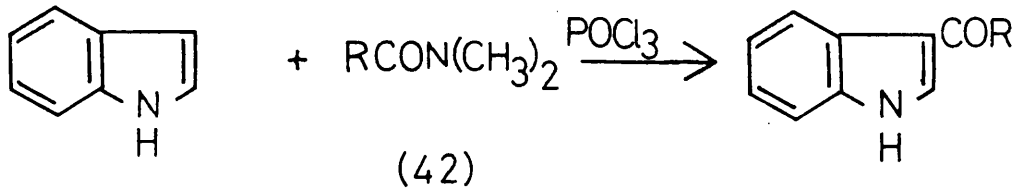


(41)

Inverse addition of the Grignard reagent to the acid chloride is necessary to prevent two molecules of indole attacking one molecule of acid chloride.

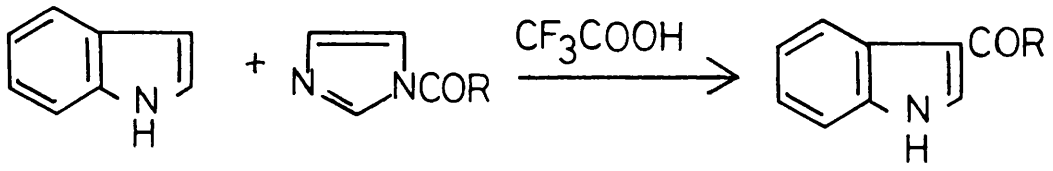
Treatment of the Grignard reagent (41) with esters generally leads to mixed 1- and 3-acylation; however certain esters give exclusively 3-acylation[41].

The Vilsmeier-Haack reaction gives 3-acylindoles by treatment of indoles with amides (42) in the presence of phosphorus oxychloride[42].



(42)

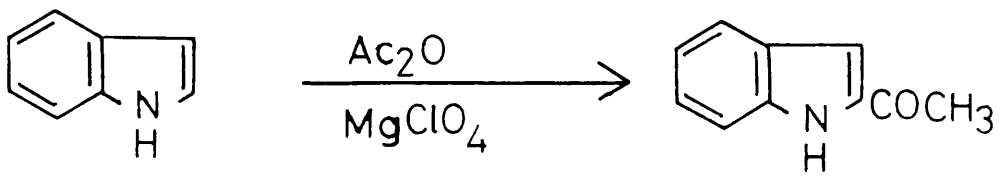
Imidazole and trifluoroacetic acid are also reported to facilitate acylation of indoles[43]. The acylimidazole (43) is prepared and reacted with indole in trifluoroacetic acid.



(43)

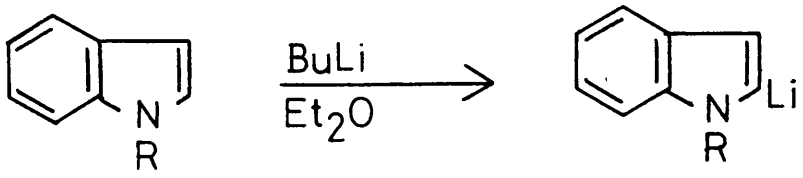
The synthesis of 2-acylindoles presents a rather greater problem. Indoles are highly reactive towards electophilic substitution at the 3-position and attack at the 2-position is more difficult.

2-Acetylindole (44) is synthesised by treatment of indole with acetic anhydride in the presence of a catalytic amount of magnesium perchlorate[44]. The catalyst is thought to bring about rearrangement of 1-acetylindole to 2-acetylindole.



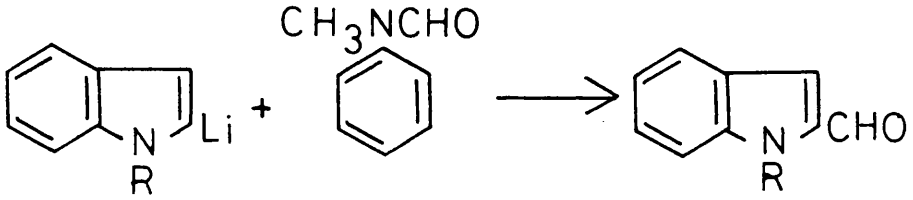
(44)

Metalation of indole with butyllithium gives 1-lithioindole; however, if the 1-position is protected the 2-lithioindole (45) results[45].



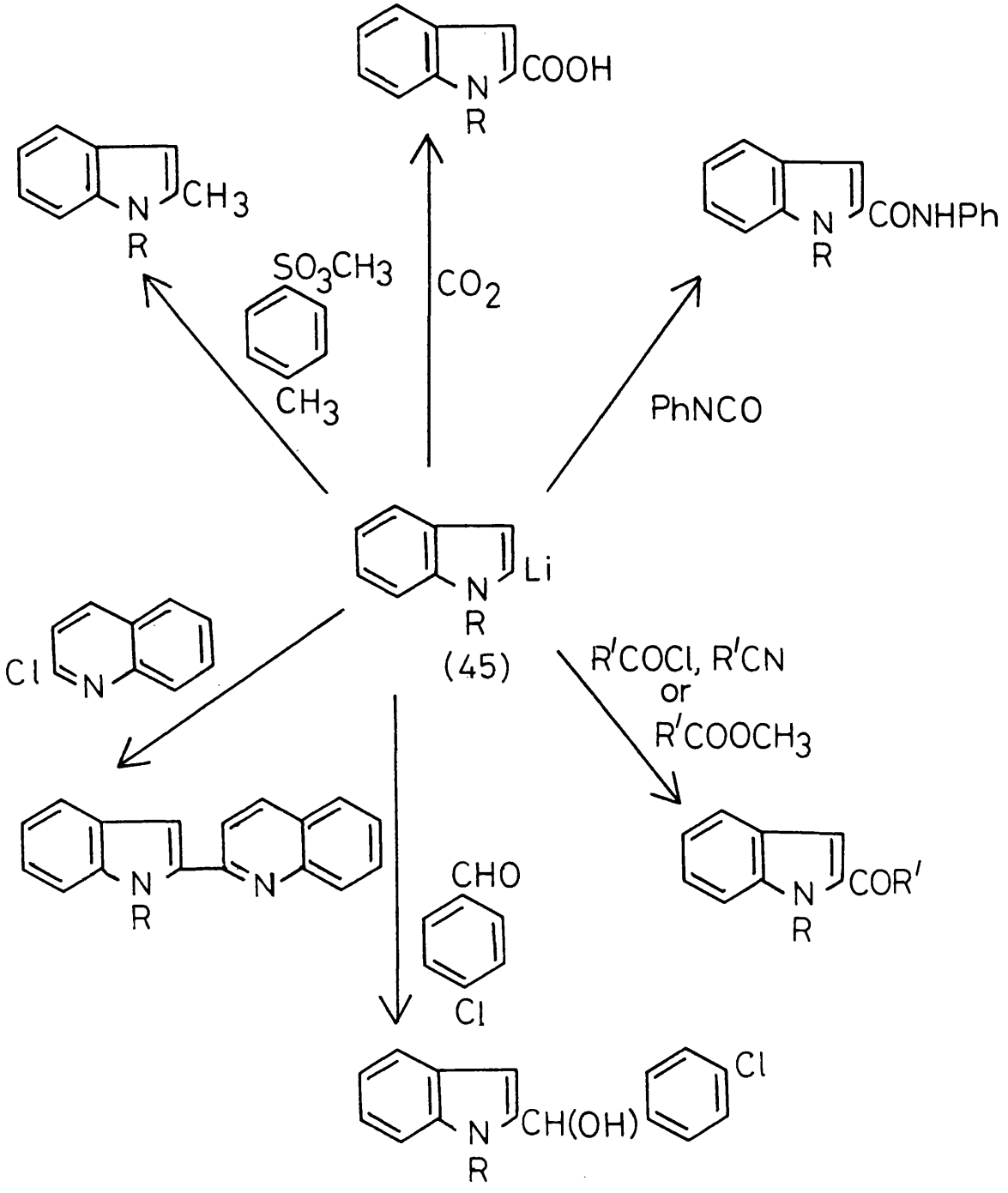
(45)

This reagent is an important intermediate in the preparation of a variety of 2-substituted indoles[46] (scheme 5) including 2-acylindoles. Treatment of (45) with N-methylformanilide (46) is a useful route to indole-2-aldehydes (47)[47].

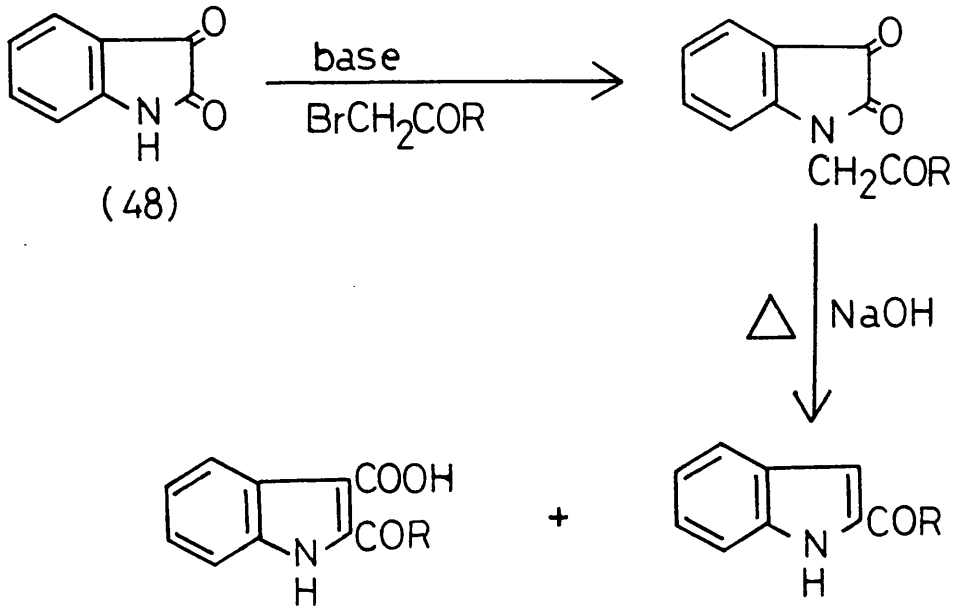


(45) (46) (47)

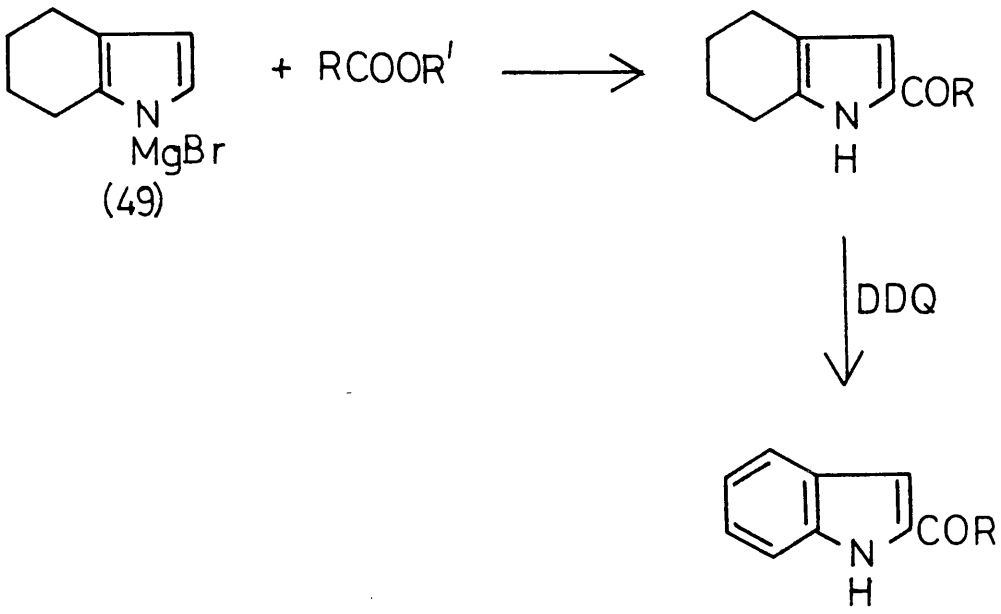
Scheme 5


COOH
N
R
CH3
SO3CH3
CH3
CO2
CONHPh
PhNCO
Li
(45)
Cl
R'COCl, R'CN
or
R'COOCH3
CHO
Cl
COR'
CH(OH)
Cl

Black[48] has recently reported a synthesis of 2-acylindoles from isatin (48).



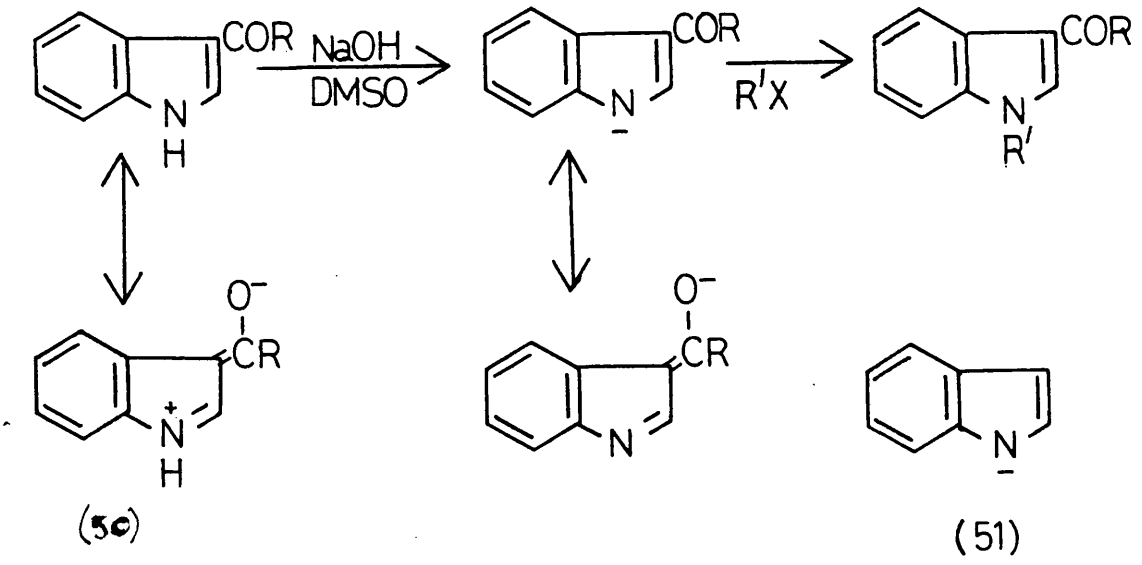
Joule[49] reports inadequacies experienced in some conventional 2-acylindole syntheses and reports a new route which was found subsequently to be of greatest synthetic value in this thesis. It has been noted that indole magnesium bromide reacts with electrophiles at the 3-position. However, pyrrole magnesium bromide is reactive at the 2-position. 4,5,6,7-Tetrahydroindole behaves as a dialkylpyrrole and is subject to electrophilic attack at the 2-position. Thus treatment of tetrahydroindole magnesium bromide (49) with esters followed by aromatisation with dichlorodicyanobenzoquinone (DDQ) gives 2-acylindoles.



Properties of Acylindoles

Strong intermolecular hydrogen bonding gives rise to the low solubility of 3-acylindoles in most organic solvents. However, rather greater solubility is seen in hydrogen bond breaking solvents such as pyridine, dimethylsulphoxide and dimethylformamide.

The indole anion (51) is formed in concentrated aqueous alkali or stronger basic systems; indoles are thus more acidic than aliphatic amines since the conjugate anion is stabilised by resonance[50]. The pK_a values of 3-acylindoles are unusually low: this relatively high acidity is caused by the intermolecular hydrogen bonding between the NH and the carbonyl group, and the strong conjugation which exists within the vinylogous amide chromophore (50). The enhanced acidity of 3-acylindoles means that they can easily be N-alkylated with alkyl halides or alkyl sulphates in the presence of moderately strong bases such as sodium hydroxide in dimethylsulphoxide[51].

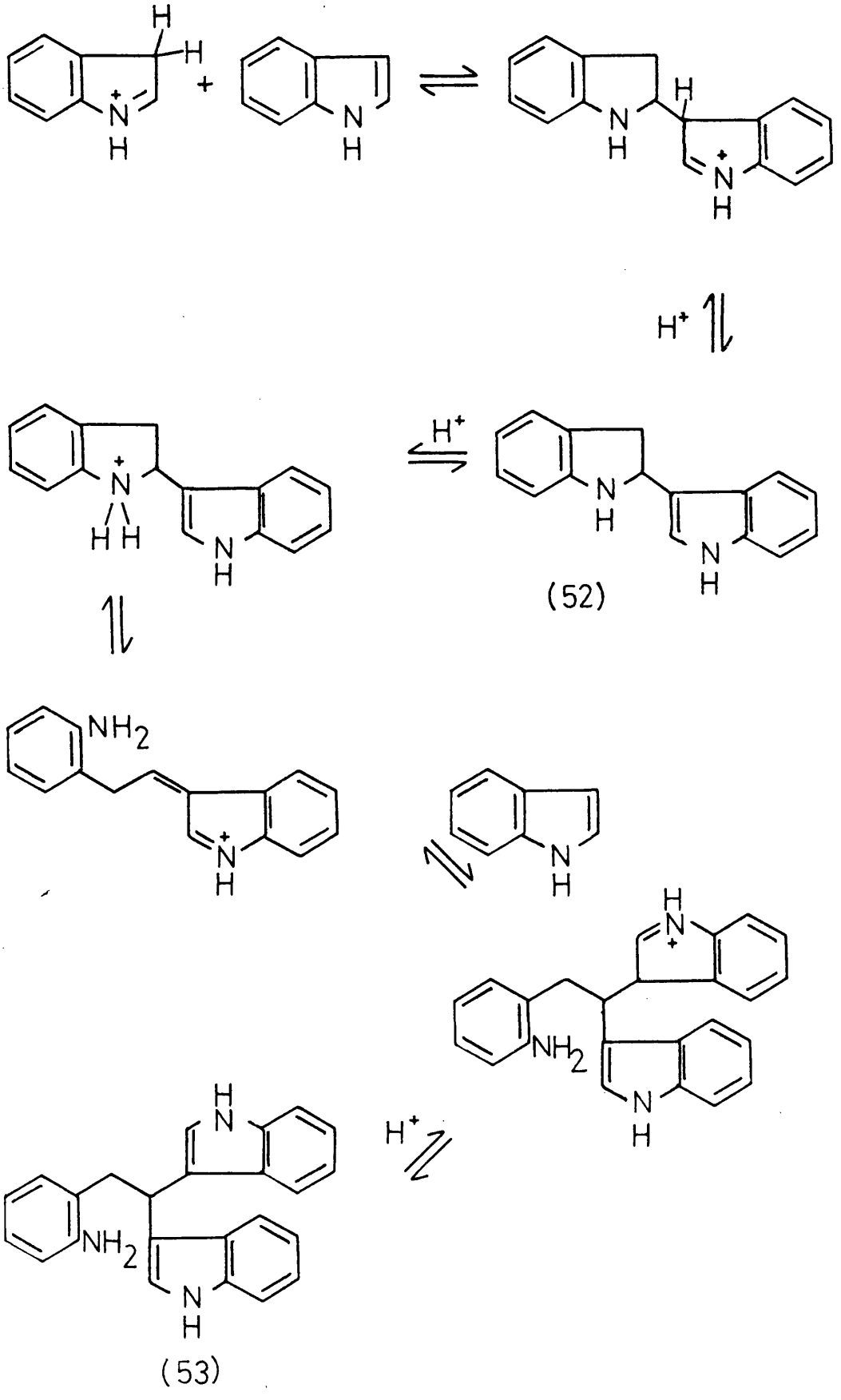


The low bond order of the carbonyl group is shown by its low infrared stretching frequency. The carbonyl group in 3-acylindoles absorbs at 1620-1590 cm^{-1}, 2-acylindoles absorb at 1630 cm^{-1}. The ring current in the pyrrole ring of indoles is less than in the benzene ring, so the protons in the 2- and 3- positions are less deshielded and appear at higher fields than the other protons in the proton magnetic resonance spectrum. The large electron density at the 3-position in simple indoles is reflected in its chemical shift (~6.4 ppm downfield from TMS). The carbonyl group in 3-acylindoles causes deshielding of the proton in the 4-position giving rise to a signal at 8.0 - 8.2 ppm. This is characteristic of 3-acylindoles; there is no corresponding effect in 2-acylindoles.

Indoles unsubstituted at the 3-position are prone to dimerisation and trimerisation[52]. Treatment of indole with dry hydrogen chloride in aprotic solvents gives the hydrochloride salt of the indole dimer (52)[53].

In aqueous acids an equilibrium is established between indole, the dimer (52), the trimer (53) and their salts (scheme 6)[54]. Both dimerisation and trimerisation are acid catalysed and their rates depend upon acid concentration; the indole is protonated at the 3-position. Dimerisation of indole accompanies certain reactions involving electrophilic substitution[55]. This tendency towards polymerisation is thought to have been a major problem in some of the oxidative reactions carried out in this thesis.

Scheme 6

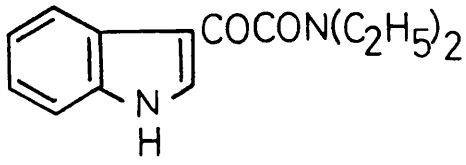


(52)

(53)

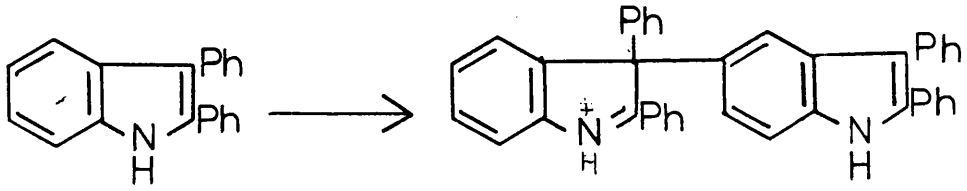
Electrochemical Oxidations of Indoles

Indole itself is oxidised at a potential of + 0.94 volts relative to the SCE[56]. Polymerisation is a major problem which causes electrode fouling and makes product isolation difficult. However, if a carbon felt anode is used with tetraethylammonium perchlorate as supporting electrolyte in acetonitrile it is possible to isolate compound (54) in 15% yield[57]. The extra atoms appear to have come from the electrolyte, but the mode of formation is not known.



(54)

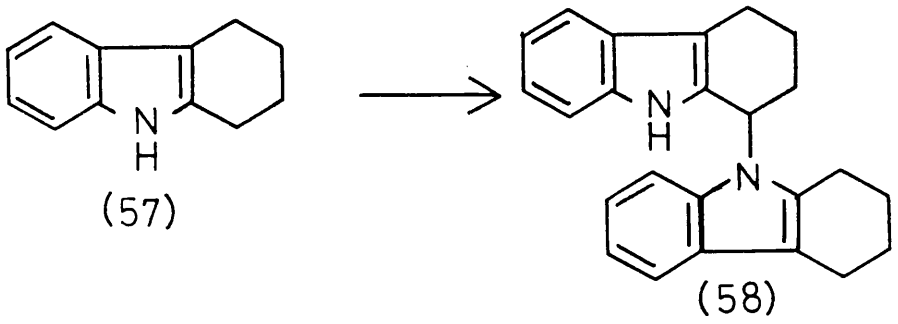
When the 2- and 3-positions of indole are blocked dimerisation occurs. Thus oxidation of 2,3-diphenylindole (55) gave (56) in 90% yield.



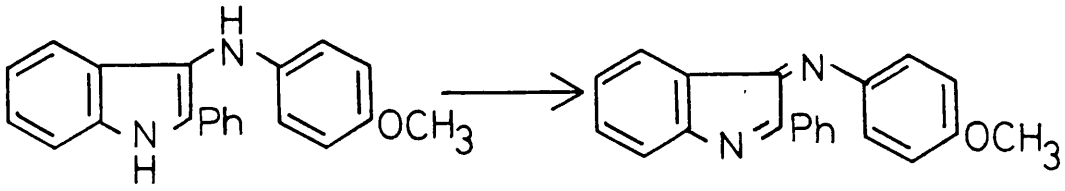
(55) (56)

On the other hand oxidation of 1,2,3,4-tetrahydrocarbazole (57) afforded the dimer (58)[59] through benzylic coupling, and electrolysis of the 3-arylaminoindole (59) yielded the 3-imino-3*H*-indole (60) through deprotonation at the exocyclic position[60].

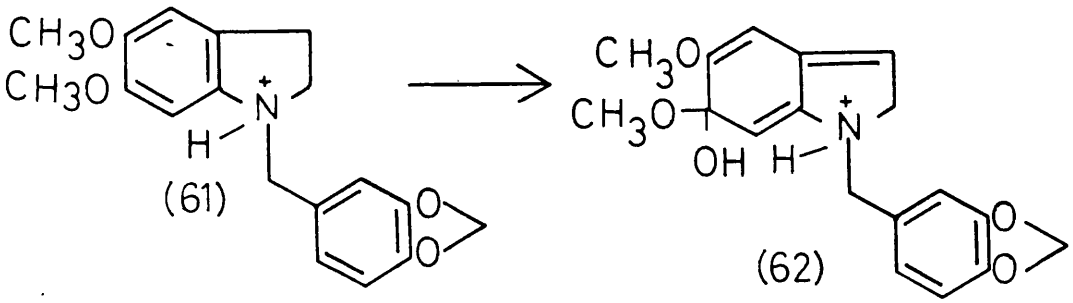
Sainsbury and Wyatt have investigated the anodic oxidation of several indole derivatives in this laboratory[61]. The indoline salt (61) gave the demethylated indole (63). The reaction intermediate is thought to be the dienol (62) which then loses methanol, since the reaction does not take place with the corresponding 5,6-methylenedioxyindoline.



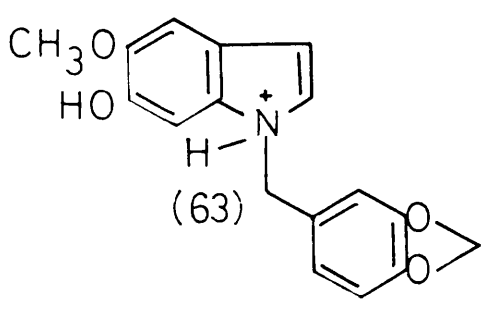
(57) (58)



(59) (60)

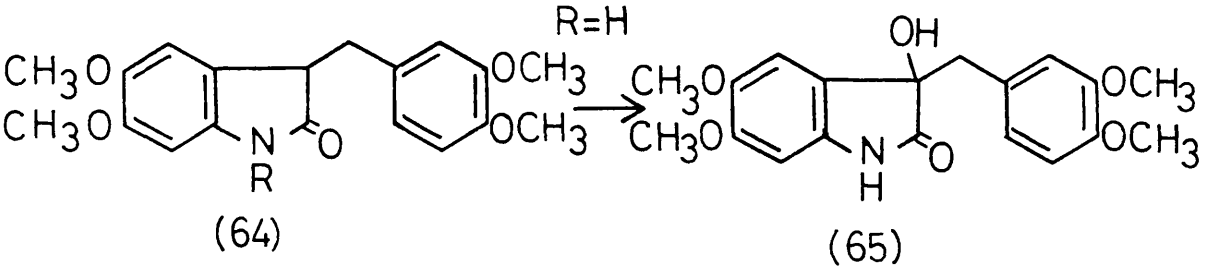


(61) (62)



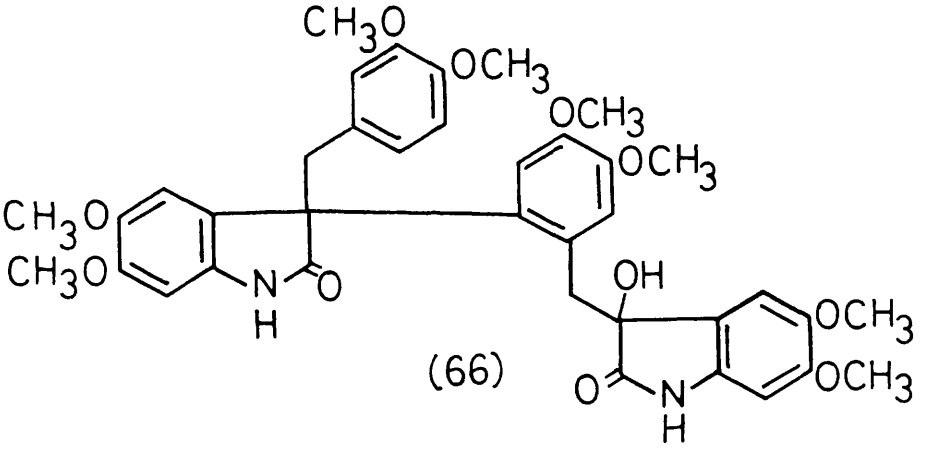
(63)

In another experiment the oxindole (64, R=H) gave two products, the 3-hydroxyoxindole (65) and the dimeric compound (66).



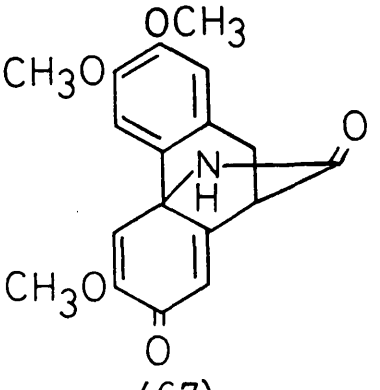
(64) (65)

+



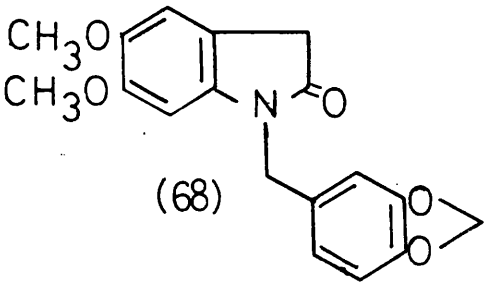
(66)

Interestingly the N-acetyl compound (64, R=$COCH_3$) undergoes intramolecular coupling to give (67) although the yield is only modest.

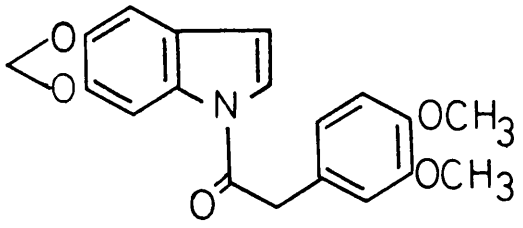


(67)

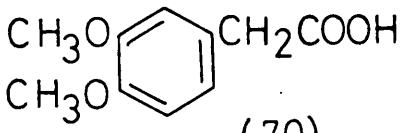
However, the N-substituted oxindole (68) only gave an intractable tar on oxidation, but in a related investigation with the N-acylindole (69) a small amount of 3,4-dimethoxyphenylacetic acid (70) was formed due to fragmentation of the N-substituent.



(68)

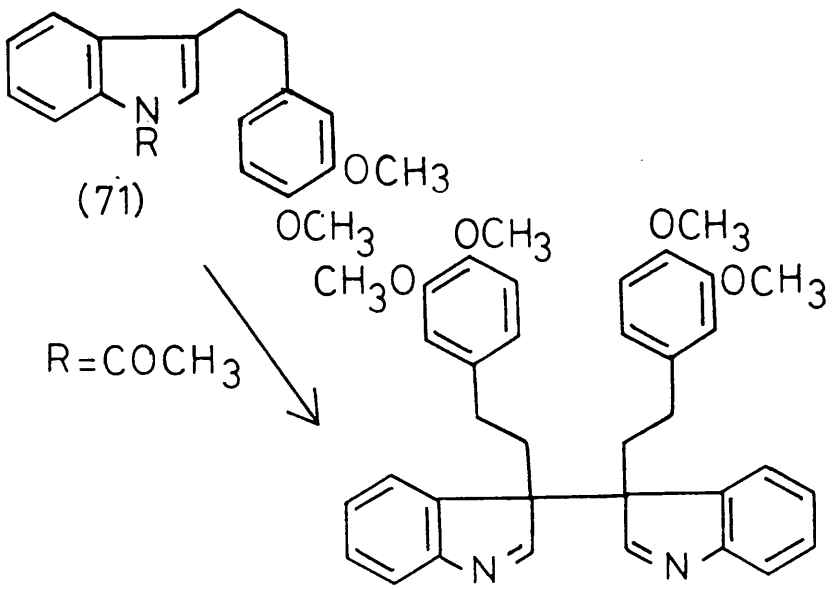


(69)



(70)

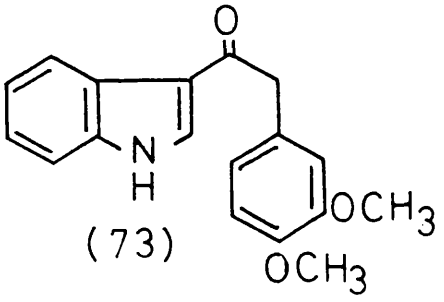
3-(3,4-Dimethoxyphenyl)ethylindole (71,R=H) gave a resin on oxidation, but the N-acetyl compound (71, R=$COCH_3$) afforded the dimer (72).



(71)

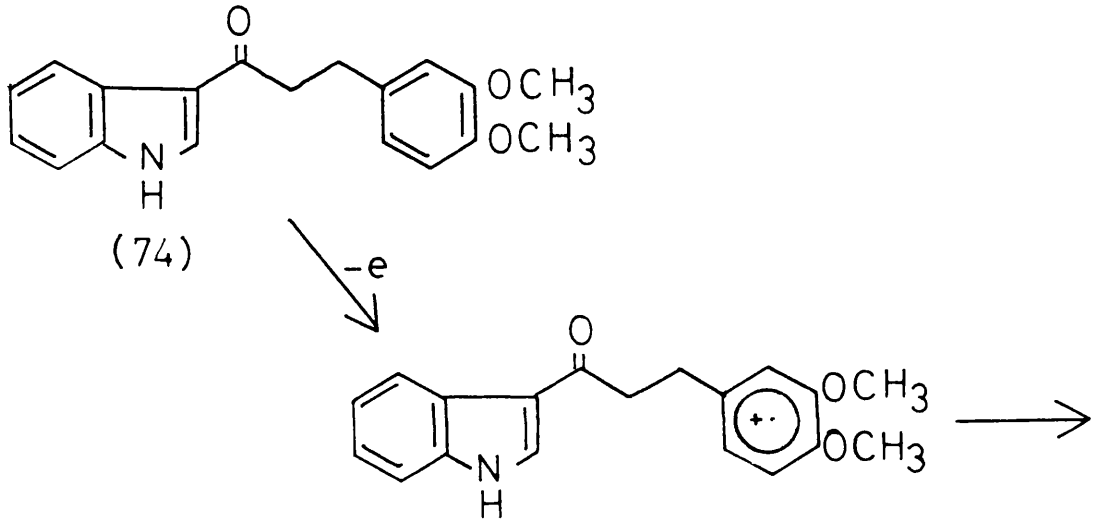
(72)

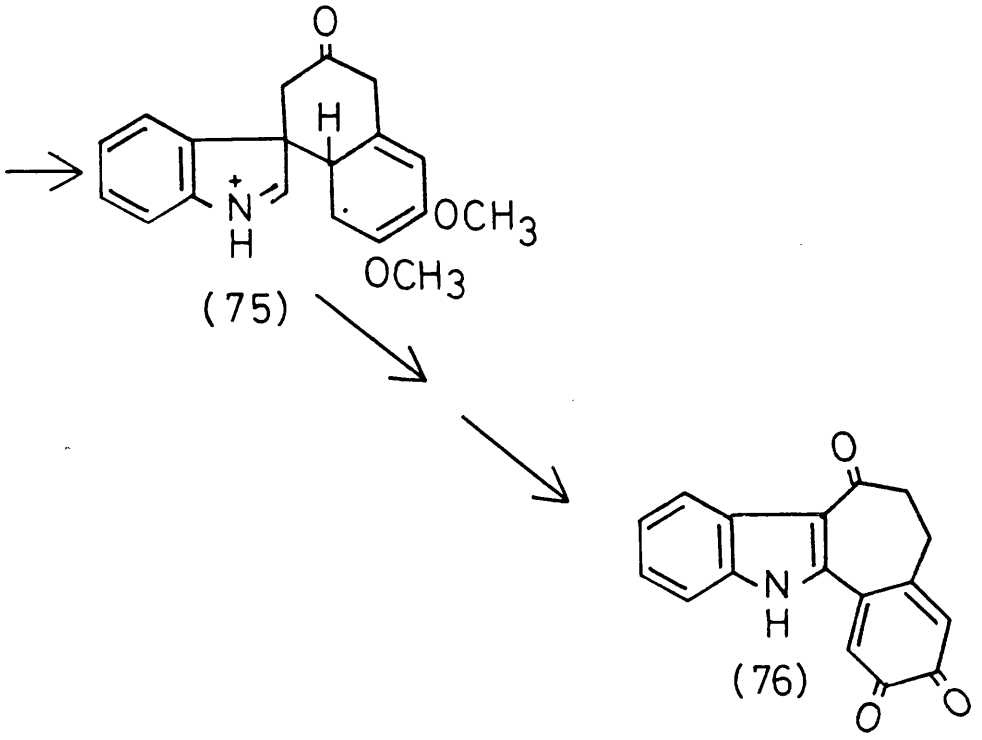
For these substrates which contain both an indole moiety and an oxygenated aromatic ring it is difficult to decide which system is oxidised first although instinctively one favours the indole nucleus. Thus, the more deactivated carbonyl compound (73) failed to undergo any reaction under electrochemical conditions and its cyclic voltammogram showed only a redox couple at + 1.2 volts. The presence of the acyl group in the 3-position raises the oxidation potential of the indole ring and so the electron loss must now be from the dimethoxyphenyl ring.



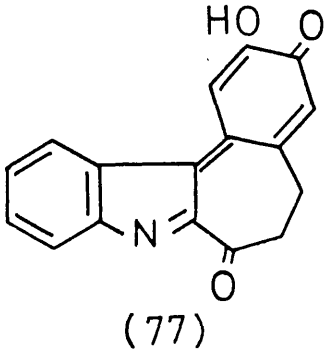
(73)

The starting point for this thesis was the anodic oxidation of compound (74) which undergoes a coupling reaction. Once again initial ionisation occurs from the aryl nucleus of the 3-substituent and this is assumed to attack the indole at the 3-position giving the spiro-intermediate (75). This was thought to rearrange and undergo further oxidation to give the quinone (76).





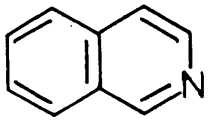
However, this product failed to react with 1,2-diamimobenzene to give a quinoxaline and did not undergo Diels-Alder reactions with a variety of dienophiles[62]. Rearrangement of (75) could also give the quinone enol (77). Such a structure would not be expected to undergo the above mentioned reactions, and so the true nature of the oxidation product was in doubt when this work began.



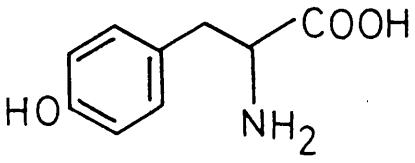
(77)

Synthetic Routes to Isoquinolines

Isoquinoline (78) was first reported in 1885[63] when it was isolated from coal tar. Many types of isoquinolines have been found in three natural sources: coal tar, petroleum and plants. By far the largest number of isoquinoline derivatives have been isolated from plants. These are the isoquinoline alkaloids which are biosynthesised from tyrosine (79).



(78)



(79)

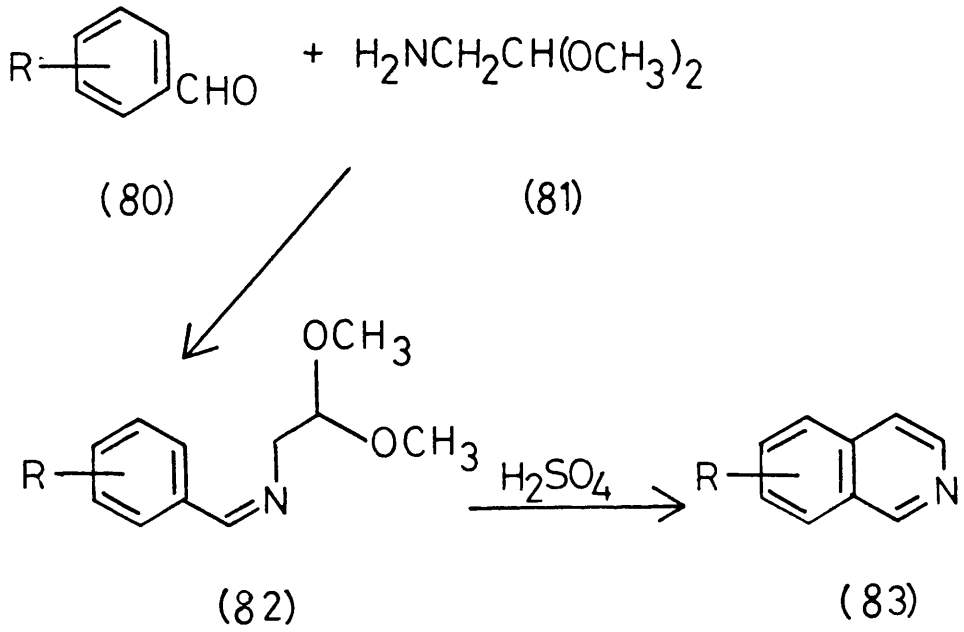
The frequent occurrence of the isoquinoline nucleus in alkaloids and in some physiologically active compounds has led to great interest in the construction of isoquinoline derivatives. The classical methods of synthesis comprise the familiar Bischler-Napieralski, Pictet-Spengler, and Pomeranz-Fritsch reactions. In recent years many modifications of these classical syntheses have been published in addition to some new synthetic routes.

In this thesis all the isoquinolines used were synthesised by modified Pomeranz-Fritsch reactions.

The Pomeranz-Fritsch Reaction

The Pomeranz-Fritsch reaction[64] is carried out in two stages. First of all an aromatic aldehyde (80) is condensed with aminoacetaldehyde dimethylacetal (81) to form a Schiff base (82). The second stage requires the acid-catalysed cyclisation of these products to the isoquinoline (83). The second step is an intramolecular electrophilic

substitution and consequently the ease of cyclisation depends on the susceptibility of the aromatic ring to electrophilic attack. If the ring is activated by electron donating substituents the cyclisation occurs under mild conditions whereas unsubstituted or deactivated substrates require higher temperatures and more acidic conditions.

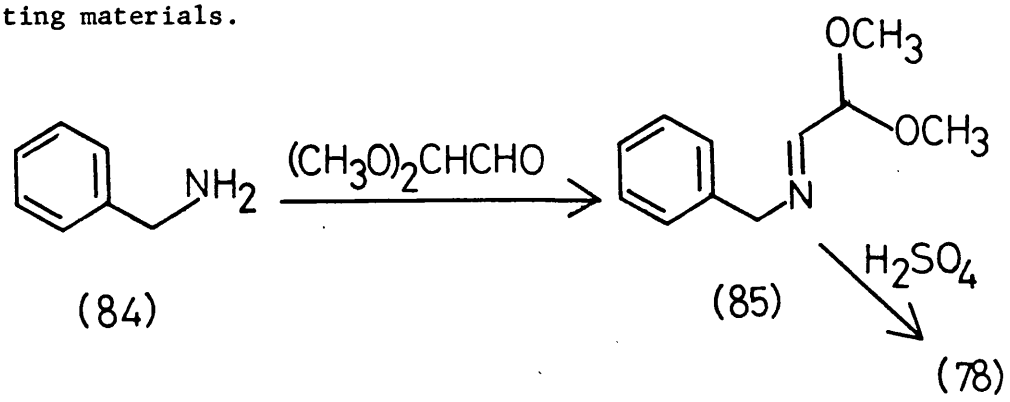


The original Pomeranz-Fritsch procedure has now largely been superseded by various modifications, some of which are outlined below.

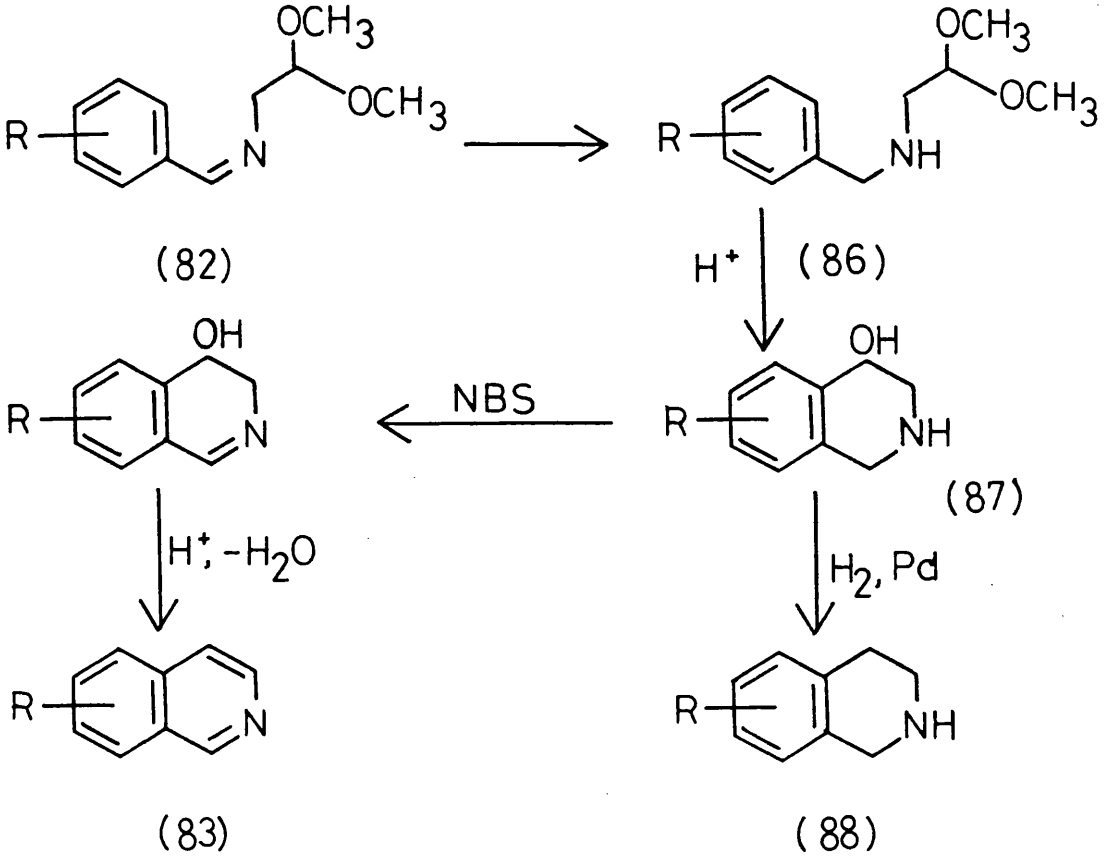
Modifications of the Pomeranz-Fritsch Reaction

Schlittler and Muller[65] condensed benzylamine (84) with glyoxal semiacetal to give the alternative Schiff base (85) which may be

cyclised with sulphuric acid to isoquinoline itself. This modification simply allows the substitution of benzylamines for benzaldehydes as starting materials.

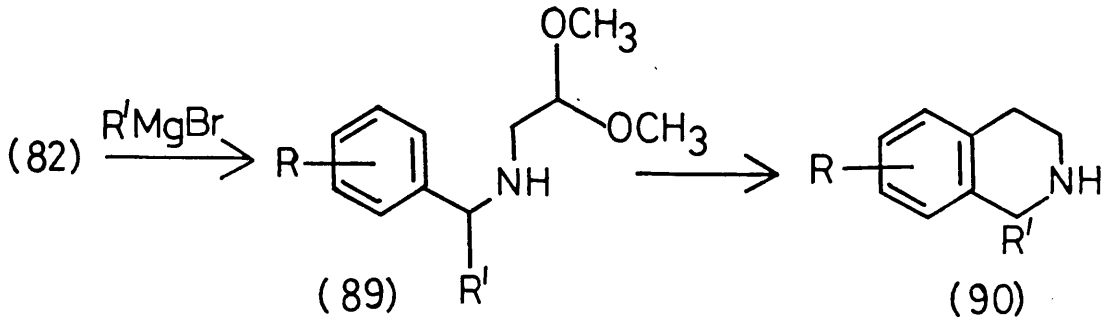


However, a much more important modification of the Pomeranz-Fritsch reaction is that pioneered by Bobbitt[66] and subsequently used by many others. Here a Schiff base (82) is reduced to a benzylamine (86) which is cyclised with 6N hydrochloric acid at room temperature to give the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (87). This compound

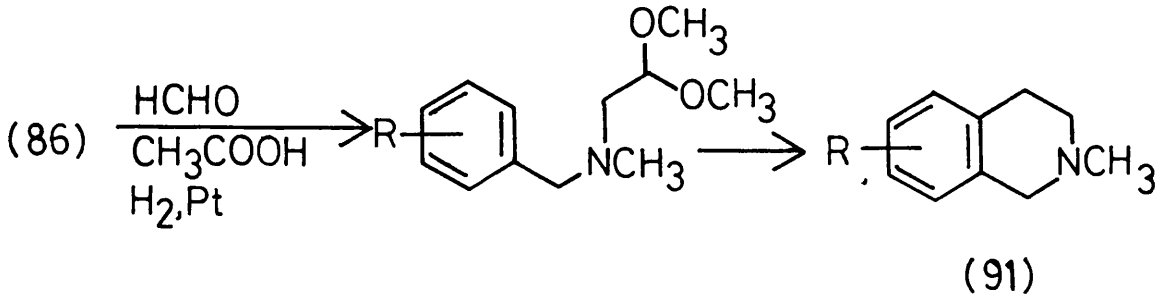


(87) is then hydrogenated to give the 1,2,3,4-tetrahydroisoquinoline (88) or treated with N-bromosuccinimide (NBS), followed by dehydration to give the fully aromatic isoquinoline (83).

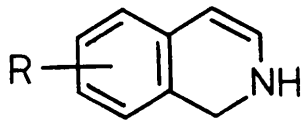
If the Schiff base (82) is treated with a Grignard reagent then the resultant benzylamine (89) affords a 1-alkyl or 1-aryl-1,2,3,4-tetrahydroisoquinoline (90) on cyclisation and reduction[67].



Reductive alkylation of the benzylamine (86) with formalin followed by the usual cyclisation yields the 2-methyl-1,2,3,4-tetrahydroisoquinoline (91)[68].

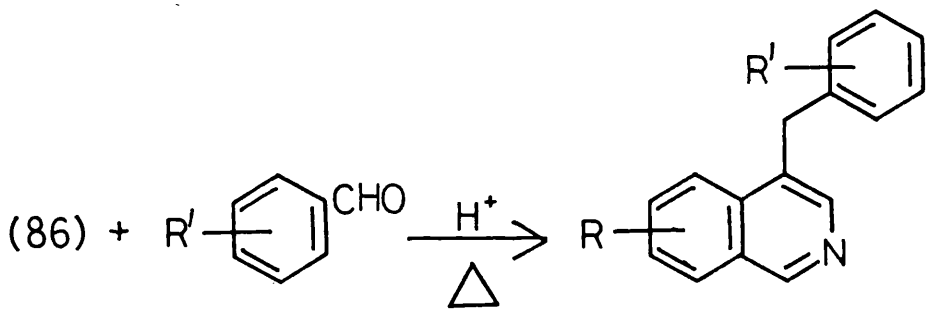


The Bobbitt synthesis is thus of general use in the preparation of 1,2,3,4-tetrahydroisoquinolines substituted at the 1,2,5,6,7- and 8- positions but if the Bobbitt reaction is carried out at elevated temperatures then dehydration of the 4-hydroxy compound (87) occurs to give the 1,2-dihydroisoquinoline (92). Such products are reactive enamines and can be utilised in the preparation of 4-substituted isoquinolines by reaction with electrophiles.



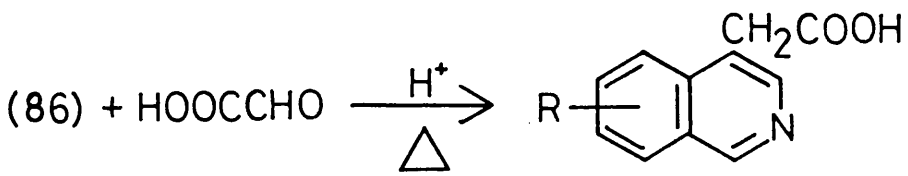
(92)

Thus cyclisation of benzylamines (86) in boiling 6N ethanolic hydrochloric acid in the presence of aromatic aldehydes yields 4-benzylisoquinolines (93)[66].



(93)

Similarly the reaction of (86) with glyoxylic acid gives 4-carboxymethylisoquinolines (94)[69].

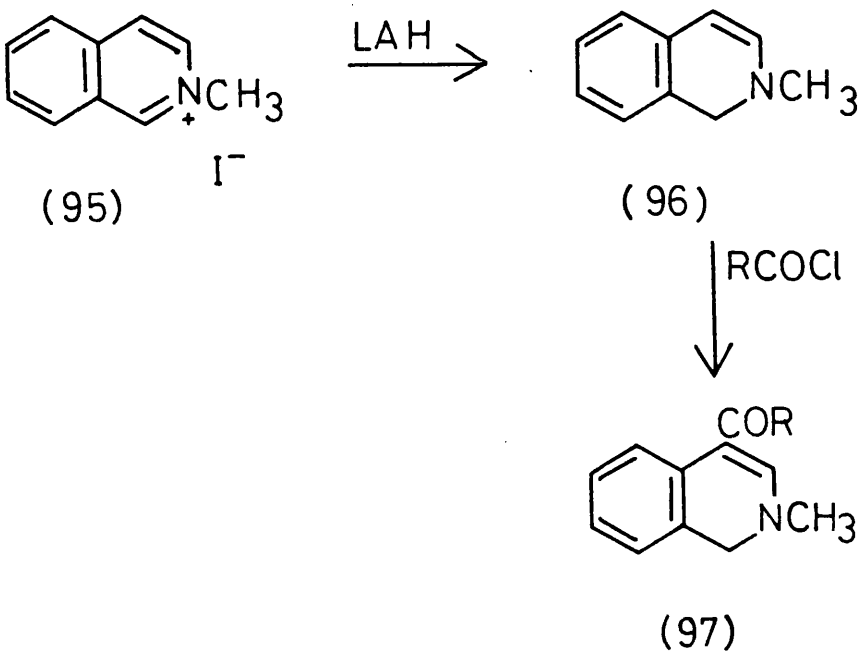


(94)

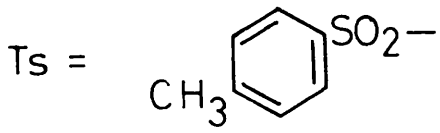
1,2-Dihydroisoquinolines can also be generated by reduction of isoquinoline salts with lithium aluminium hydride (LAH). The reactive products can then be treated with electrophiles to give 4-substituted

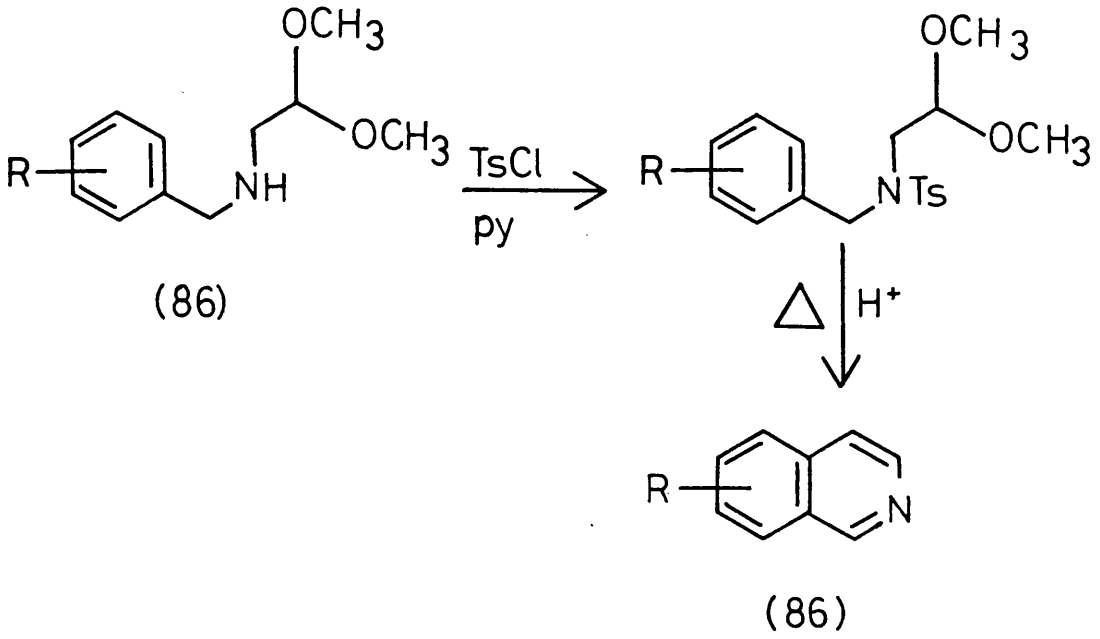
isoquinolines. This method is used here in the synthesis of 4-acyl-1,2-dihydroisoquinolines.

The methiodide (95) was reduced with LAH in ether to give 1,2-dihydro-2-methylisoquinoline (96) which was treated with acid chlorides in the presence of triethylamine to give 4-acyl-1,2-dihydroisoquinolines (97).



A further modification of the Bobbitt reaction often used in this thesis was that proposed by Jackson[70]. In this a benzylamine (86) is tosylated and then treated with acid in refluxing dioxan whereupon cyclisation occurs with the elimination of *p*-toluenesulphinic acid to give the corresponding isoquinoline (83) directly.





(86) (86)

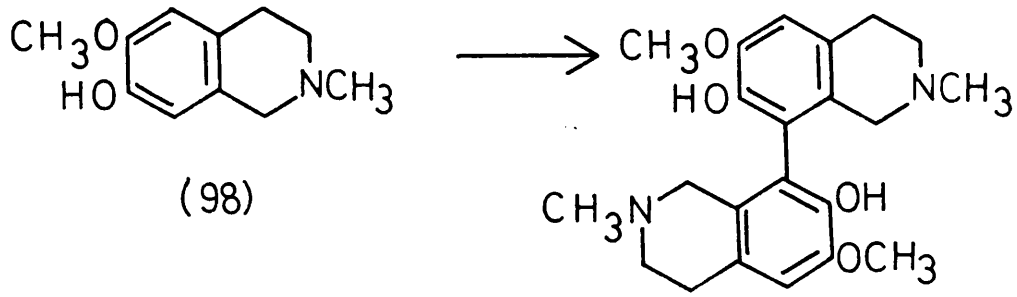
Treatment of Schiff bases (82) with boron trifluoride in trifluoroacetic anhydride also gave isoquinolines (83)[71], and this modification is useful when the isoquinoline (83) carries an alkoxy group in the 7-position.

The latest improvement of the Pomeranz-Fritsch reaction to be published is that of Watanabe[72]. Here a benzylamine (86) is treated with cold chlorosulphonic acid and cyclised to the isoquinoline (83) directly. This technique has been applied to isoquinolines substituted in the 1,6 and 7-positions in yields ranging from 15% to 75%. In general, the yields are best when the isoquinoline does not contain an alkoxy substituent in the 6 or 7-position.

Electrochemical Oxidations of Isoquinolines

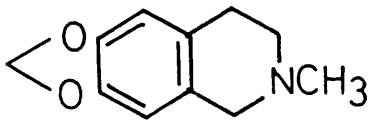
The electrochemical oxidation of isoquinoline derivatives falls into two sections, namely the oxidation of phenolic and nonphenolic compounds. Phenolic oxidation is an important field in organic chemistry and the electrochemistry of phenolic compounds often varies somewhat to the types previously encountered. Phenols are very easily oxidised and thus intermolecular coupling is very facile, so much so that ionisation

is possible in aqueous media. An example which illustrates this in point is the electrochemical oxidation of corypalline (98) which yields the dimer (99) at very low anode potential[73]. By contrast the methylenedioxy analogue (100) fails to enter into any coupling reactions under similar reaction conditions[74].



(98)

(99)



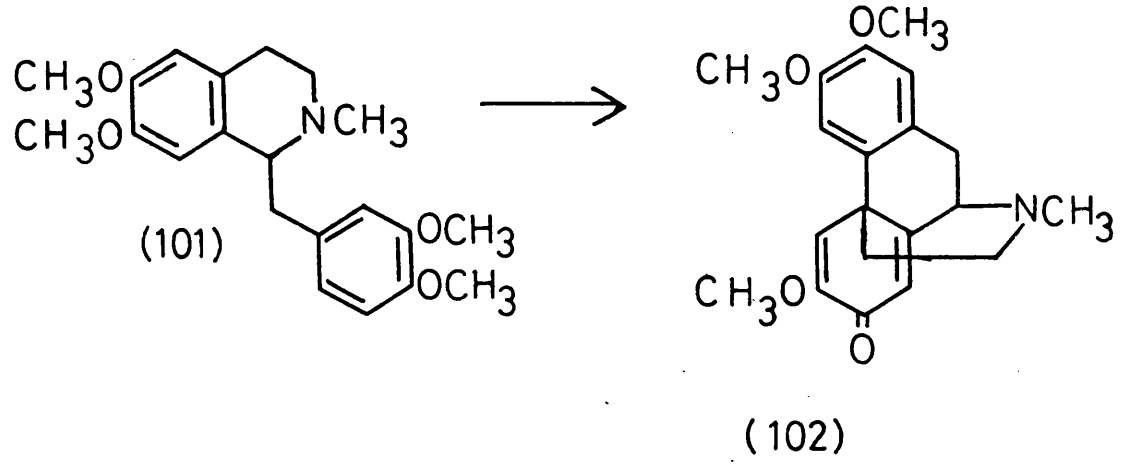
(100)

In general, tetrahydroisoquinolines form stable redox couples under electrochemical conditions due to ionisation of the nitrogen lone pair electrons.

In this thesis all the isoquinoline derivatives studied were nonphenolic and contained the 3,4-dimethoxyphenyl group which was oxidised at a potential of approximately + 1.2 volts relative to the SCE.

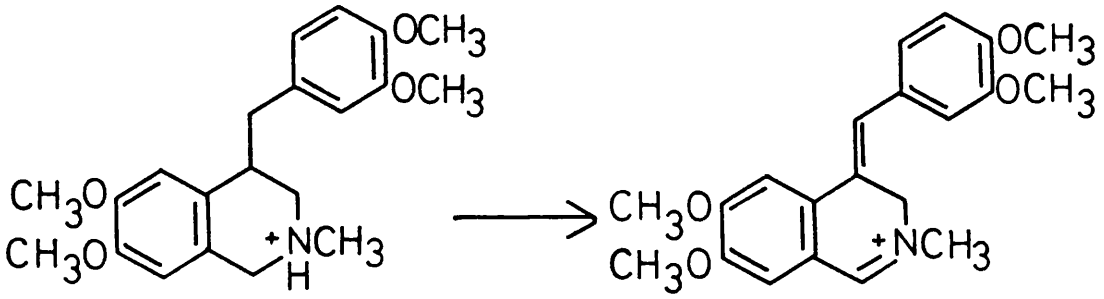
The most widely studied nonphenolic anodic oxidation in the isoquinoline field is the reaction of landanosine (101) to give the

morphinandienone alkaloid O-methylflavinantine (102)[75].



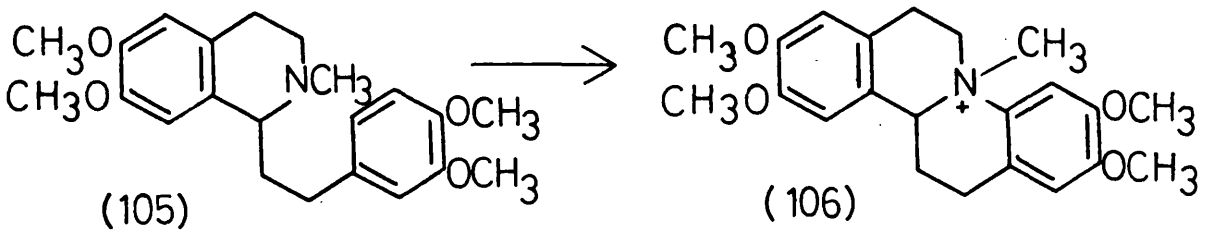
(101) (102)

Electrolysis of the 4-benzyl isomer as its hydrochloride salt (103) gave an oxidised product (104)[76] but no coupling occurred.

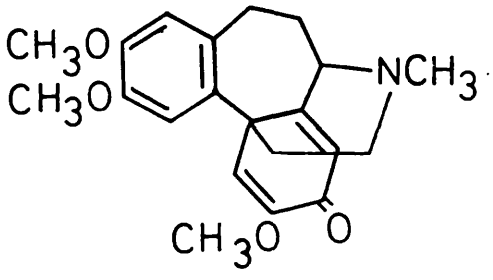


(103) (104)

Similarly anodic oxidation of the 1-phenethyltetrahydroisoquinoline (105) gave rise to the tetracycle (106)[77]. This product was unexpected; it had been anticipated that the oxidation would give rise to the androcymbine derivative (107) by a spirodienone route analogous to that for landanosine.

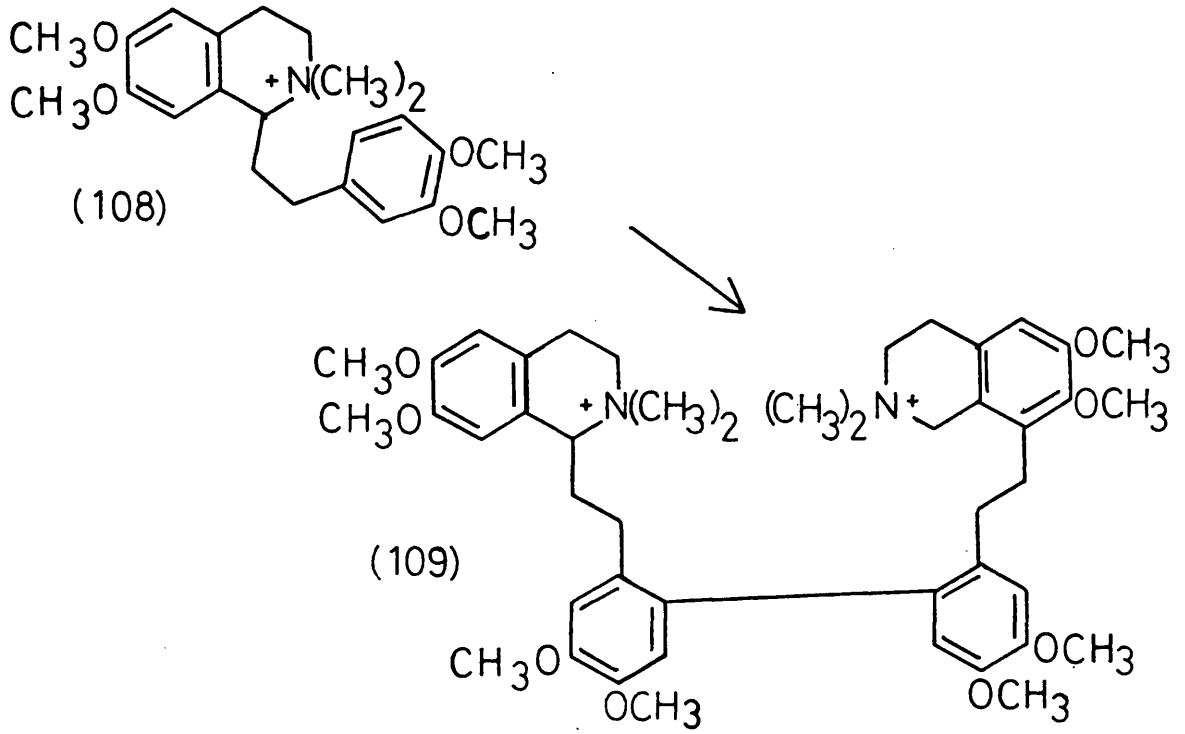


(105) (106)



(107)

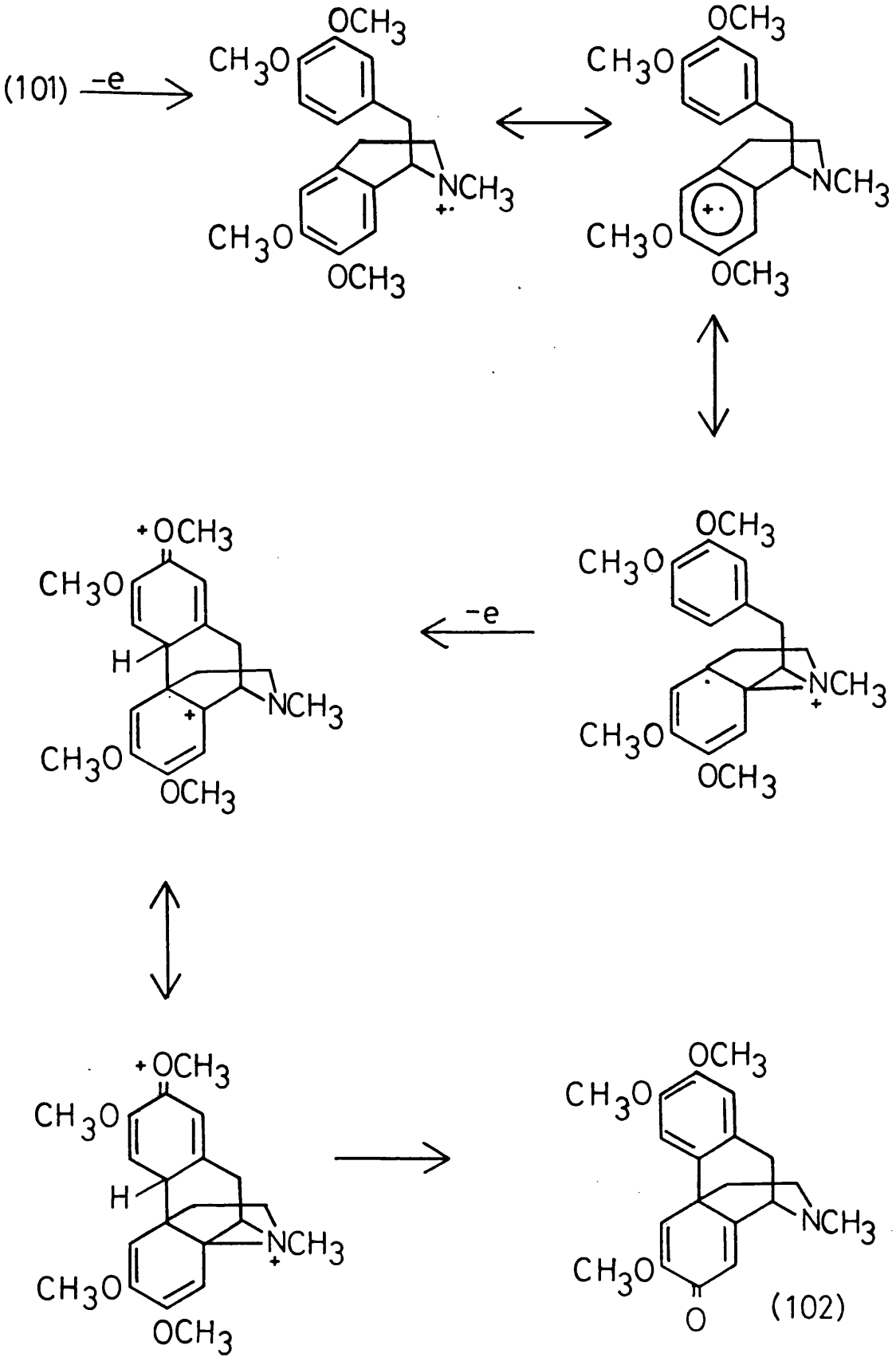
Oxidation of the methoperchlorate salt (108) of (105) also failed to give a spirodienone, the dehydrodimer (109) being the only isolated product.



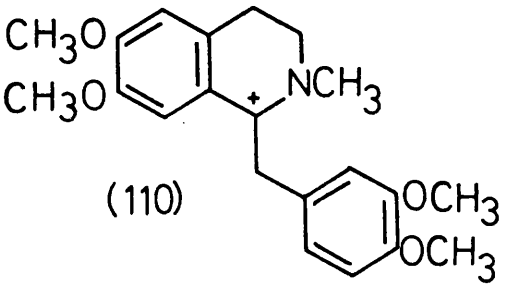
(108) (109)

Examination of the structure of landanosine (101) reveals that it contains the tetramethoxybibenzyl fragment. It was originally assumed that a similar mechanism applied to the oxidation of landanosine (101) and the bibenzyl(1)[75], namely oxidation of one of the dimethoxyaryl rings at approximately + 1.1 volts. However, it has been shown[78] that O-methylflavinantine (102) is formed in the same yield at a potential of only + 0.55 volts corresponding to oxidation of the tertiary amine function. In view of this a mechanism has been proposed (scheme 7) involving anchimeric assistance by the amine function in the annelation of landanosine. Additionally oxidation of landanosine at + 1.3 volts was shown to yield unidentified products resulting from overoxidation.

Scheme 7



Another possible mechanism analogous to scheme 3 would involve a benzylic cation intermediate (110). This however, has been disproved by Miller[79] who demonstrated retention of configuration and 95% isotopic retention in the anodic oxidation of 1-deuterolandanosine (111).



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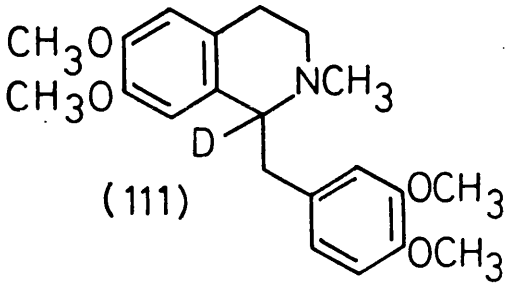
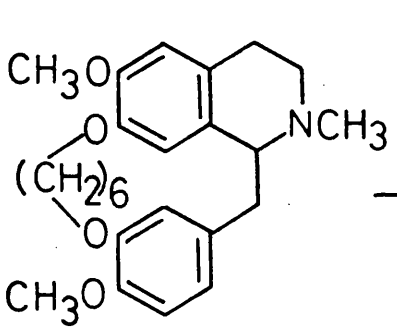
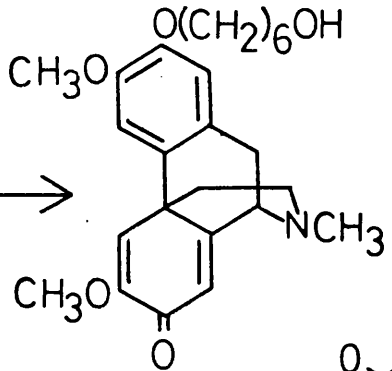


(111)

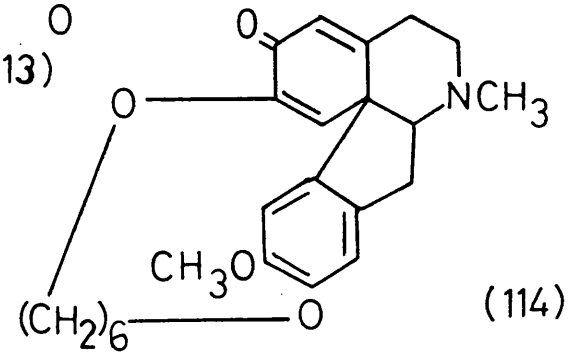
A spirodienone product (113) was also found to result from the electrochemical oxidation of the bridged ether derivative of reticuline (112)[80]. However, due to steric restriction between the two aromatic rings this was the minor product, the major component being the proerythrinadienone type compound (114).



(112)



(113)



(114)

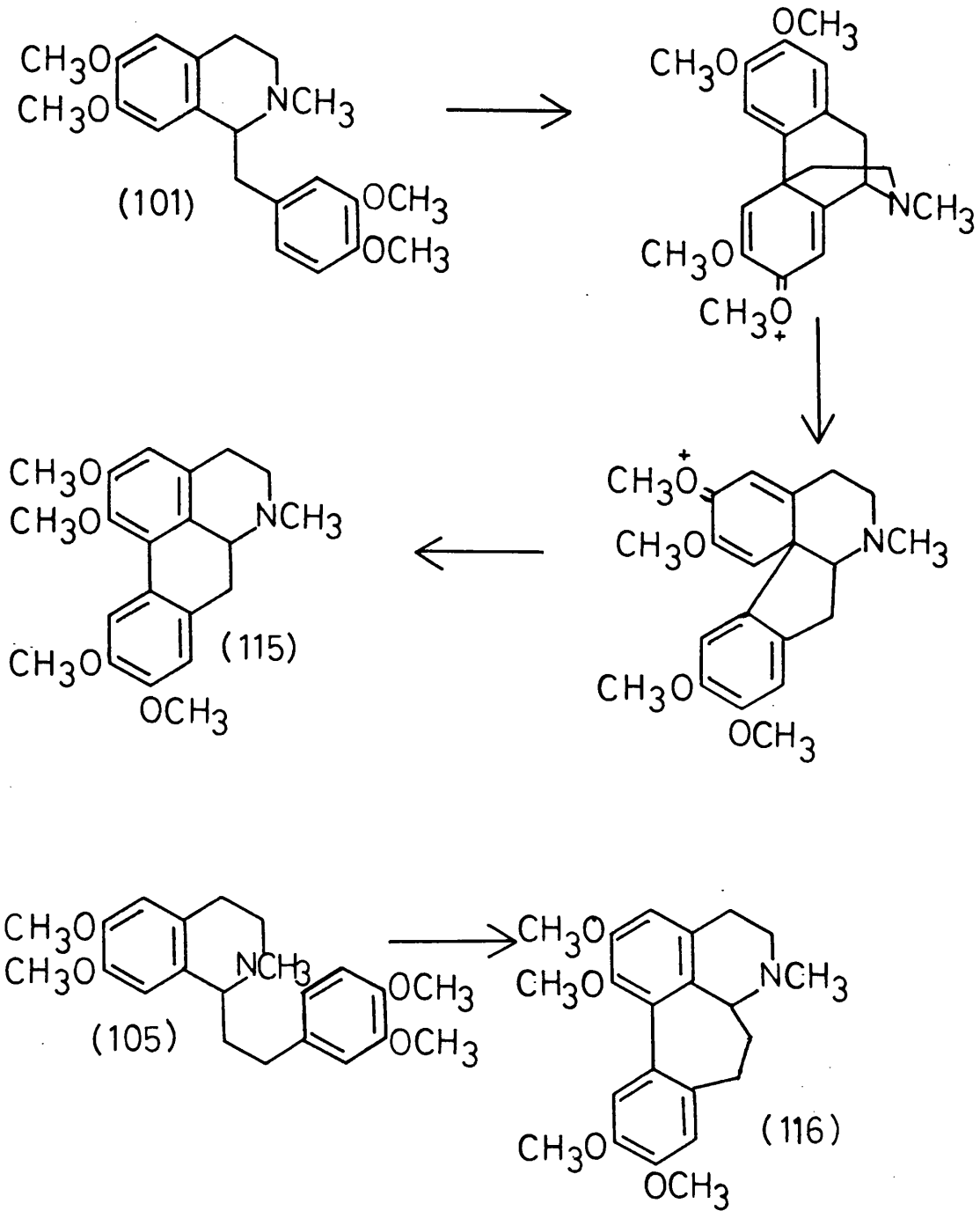
The Use of Chemical Oxidants in Coupling Reactions

In the past few years there has been an upsurge in the use of chemical electron transfer reagents to effect non phenolic oxidative coupling of aryl systems. The two most important reagents to have emerged are vanadium (V) oxyfluoride and thallium (III) trifluoroacetate. These reagents can act as one electron oxidants and so mimic anodic reactions by the generation of radical cations.

An example of the use of vanadium oxyfluoride is the oxidation of landanosine (101) to glaucine (115) in trifluoroacetic acid (TFA) *via* a morphinandienone intermediate[81] (scheme 8). It will be recalled that the morphinandienone (102) was the electrochemical product in an analogous reaction but here this is further oxidised by the chemical reagent.

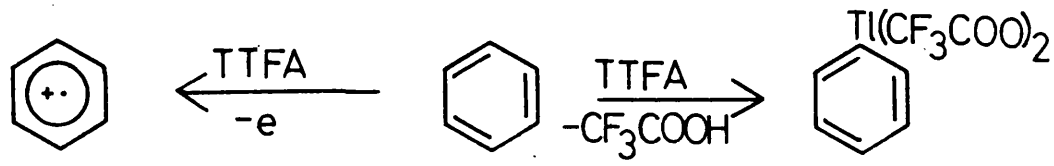
Similarly, oxidation of the 1-phenethyltetrahydroisoquinoline (105) with vanadium oxyfluoride gave the homoaporphine (116)[82].

Scheme 8


CH3O
CH3O
NCH3
(101)
OCH3
OCH3
OCH3
CH3O
NCH3
CH3O
CH3O
+
CH3O
CH3O
NCH3
CH3O
OCH3
CH3O
CH3O
NCH3
(115)
CH3O
OCH3
CH3O
CH3O
NCH3
(105)
OCH3
OCH3
CH3O
CH3O
NCH3
CH3O
(116)
OCH3

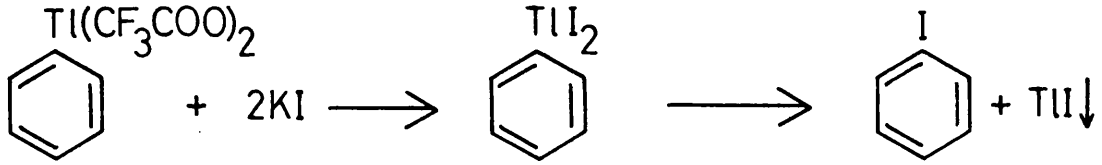
The use of thallium trifluoroacetate (TTFA) presents a problem in so far as metalation of an aryl ring[83] and oxidation to the radical cation are competing reactions (scheme 9).

Scheme 9



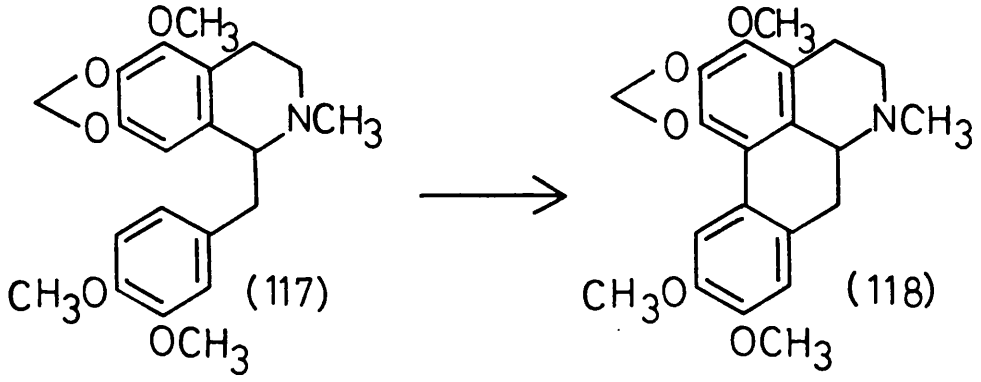
For aryl rings with low oxidation potentials, such as dimeth - oxyphenyl rings, the one electron oxidation predominates and metalation is a minor event, but the metalation reaction has been used in the synthesis of aryl iodides (scheme 10)[84].

Scheme 10

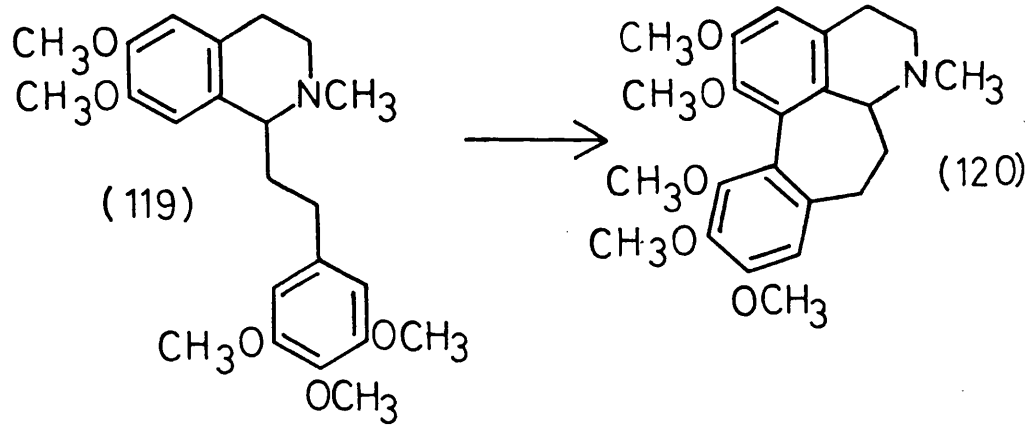


More recently the one electron reaction has been applied to the synthesis of biaryls[85] and intramolecular oxidative coupling reactions. Many of the reactions have been carried out on phenolic substrates and in these cases the phenoxonium ion plays an important role in the presumed mechanistic sequence. However, TTFA can also be applied to coupling reactions on non phenolic substrates. For example, treatment of the 1-benzyltetrahydroisoquinoline (117) with TTFA in acetonitrile

and carbon tetrachloride at -40° in the presence of a catalytic amount of boron trifluoride etherate gave the aporphine alkaloid ocoteine (118)[86].



Again, treatment of the 1-phenethyltetrahydroisoquinoline (119) with TTFA in trifluoroacetic acid and dichloromethane gave O-methyl-kreysigine (120)[87].

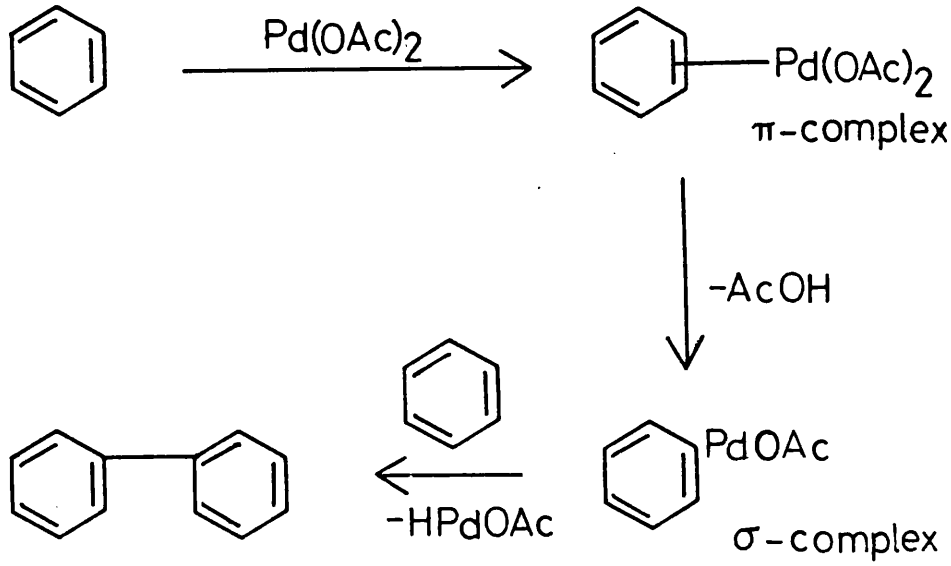


It is interesting to note that TTFA also effected the oxidation of tetramethoxybibenzyl (1) to tetramethoxyphenanthrene (3) by a route analogous to the anodic oxidation.

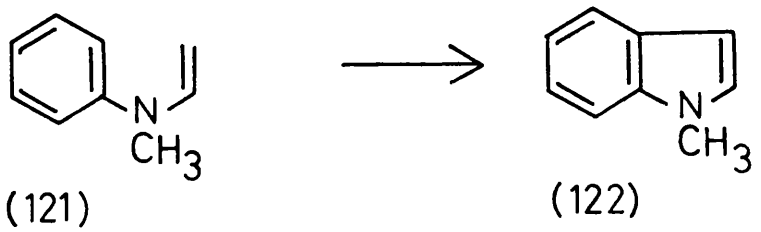
Another oxidant which has been used in coupling reactions is palladium (II) acetate. The mechanism with this reagent involves palladation of an aromatic ring to form a σ-complex. In the case of thallation with TTFA, the σ-complex is stable and can be isolated, but the corresponding palladium complex is unstable and is easily decomposed

to give biaryl formation or intramolecular coupling in a concerted mechanism[88]. The first use of palladium acetate was the synthesis of biphenyl from benzene (scheme 11)[89].

Scheme 11

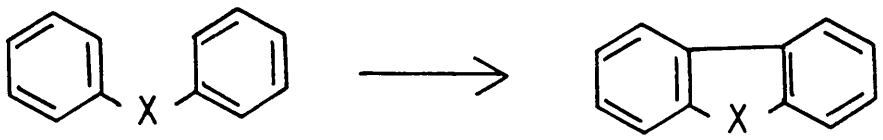


The first reported intramolecular reactions were the syntheses of heterocycles from aryl alkenes[90]. For example, the enamine (121) was cyclised by palladium acetate to give 1-methylindole (122).



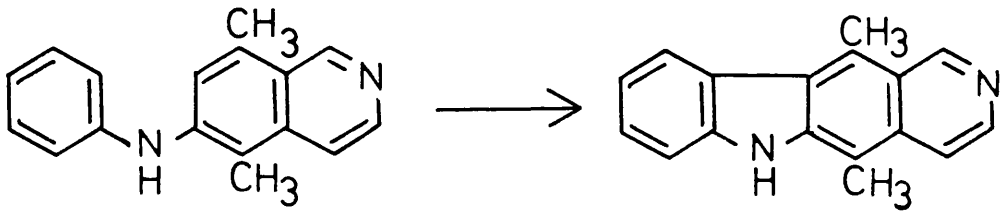
(121) (122)

Eberson[91] found that palladium acetate effected the cyclisation of diphenyl ether (123, X=O) to dibenzofuran (124, X=O), diphenylamine (123, X=NH) to carbazole (124, X=NH), and benzophenone (123,X=CO) to fluorenone (124, X=CO).

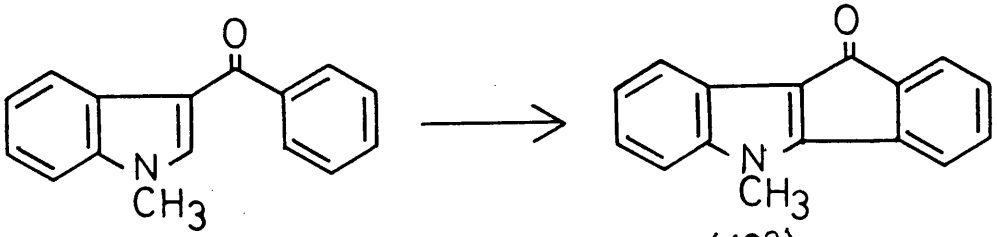


(123) (124)

This reaction has been applied to the synthesis of the pharmacologically active indole alkaloid ellipticine (126) from the diarylamine (125)[92] and Itahara has carried out palladium acetate promoted coupling reactions on benzoylindoles. Thus treatment of 3-benzoyl-1-methylindole (127) with palladium acetate in boiling acetic acid gave the compound (128)[93].

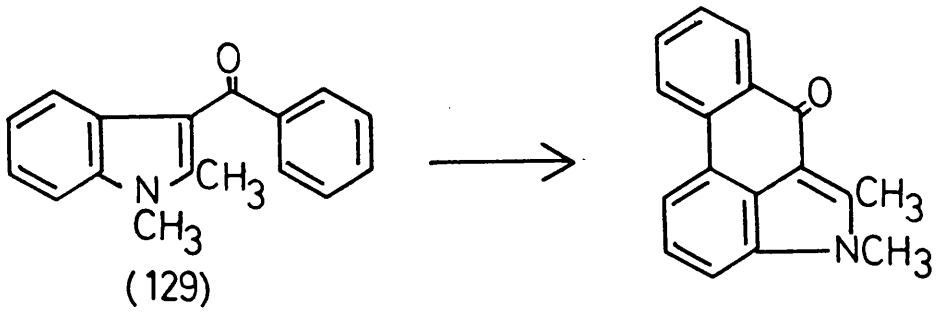


(125) (126)



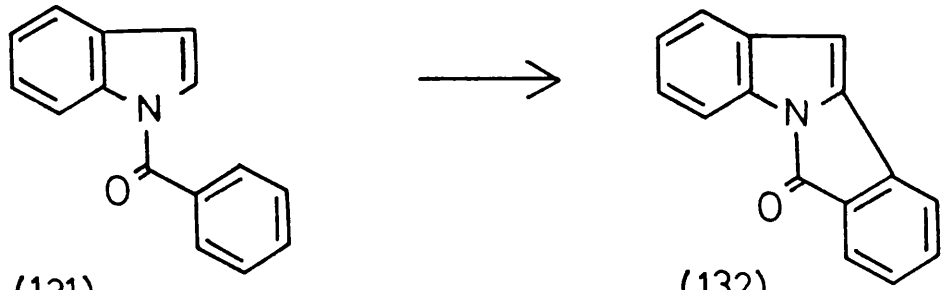
(127) (128)

If the 2-position was blocked as in compound (129) then the dihydronaphthoindolone (130) resulted[93].



(129) (130)

Treatment of 1-benzoylindole (131) with palladium acetate gave the tetracyclic compound (132)[94].



(131) (132)

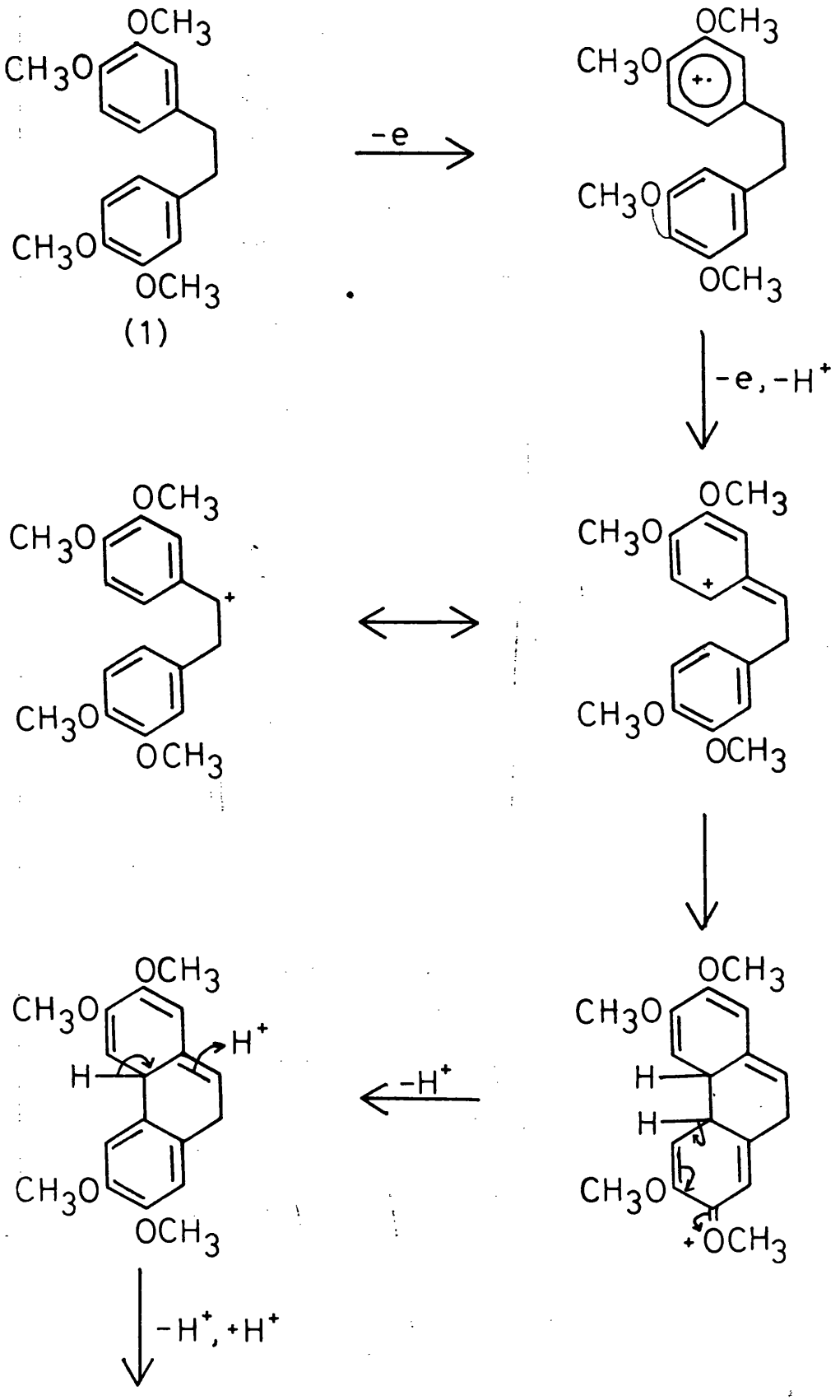
In this thesis selected chemical reactions have been carried out with palladium acetate and thallium trifluoroacetate and compared with the results from anodic oxidations.

DISCUSSION

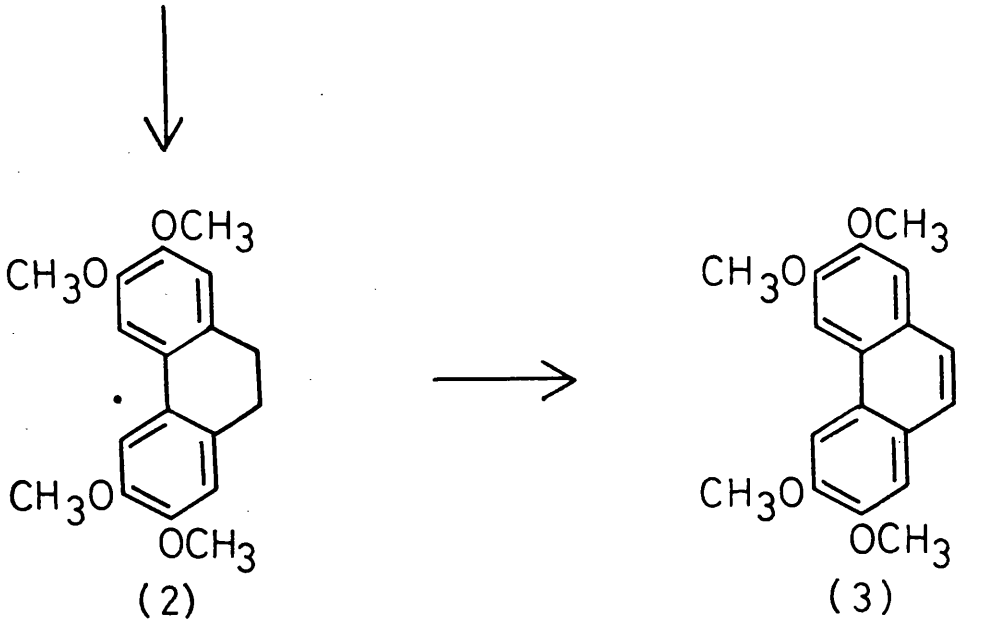
It was noted in the introduction to this thesis that anodic oxidation of 3,3',4,4'-tetramethoxybibenzyl (1) gives rise to the phenanthrene (3), and that there exists the possibility of a mechanism involving "benzylic cations" (133) as intermediates (scheme 12). If the electrolysis is carried out with 20% trifluoroacetic acid in dichloromethane as electrolyte, phenanthrene (3) is formed in quantitative yield[1]. If the electrolyte used is 0.1 M sodium perchlorate in dry acetonitrile then the yield of phenanthrene (3) is lower and most of the bibenzyl (1) is returned unchanged[2]. In this mechanism the formation of the intermediate dihydrophenanthrene (2) from the cation (133) involves the abstraction of a proton from the electrolyte, either from trifluoroacetic acid or from water which is known to be present to the extent of 10^{-2} mol.dm.$^{-3}$ in "dry" acetonitrile. If the electrolyte contained not protons but deuterons in the form of deuterotrifluoroacetic acid or deuterium oxide and if the postulated mechanism was valid then the dihydrophenanthrene (134) formed would contain a deuterium atom. Even if over oxidation to the phenanthrene cannot be prevented this incorporation should still be recognised since operation of the isotope effect should favour the formation of the 9-deuterophenanthrene (135).

As an early introduction to electro-organic chemistry an electrolysis of the bibenzyl (1) was carried out in the presence of deuterated solvents in an attempt to validate the proposed mechanism and we considered that the presence of deuterium atoms in the product would be clearly shown by mass spectrometry. Again, on the practical side the use of deuterotrifluoroacetic acid as a solvent would have

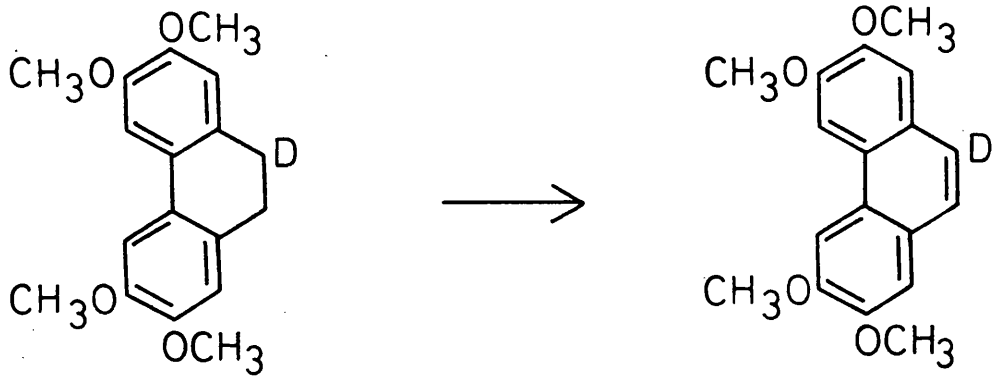
Scheme 12



Scheme 12



(2) (3)



(134) (135)

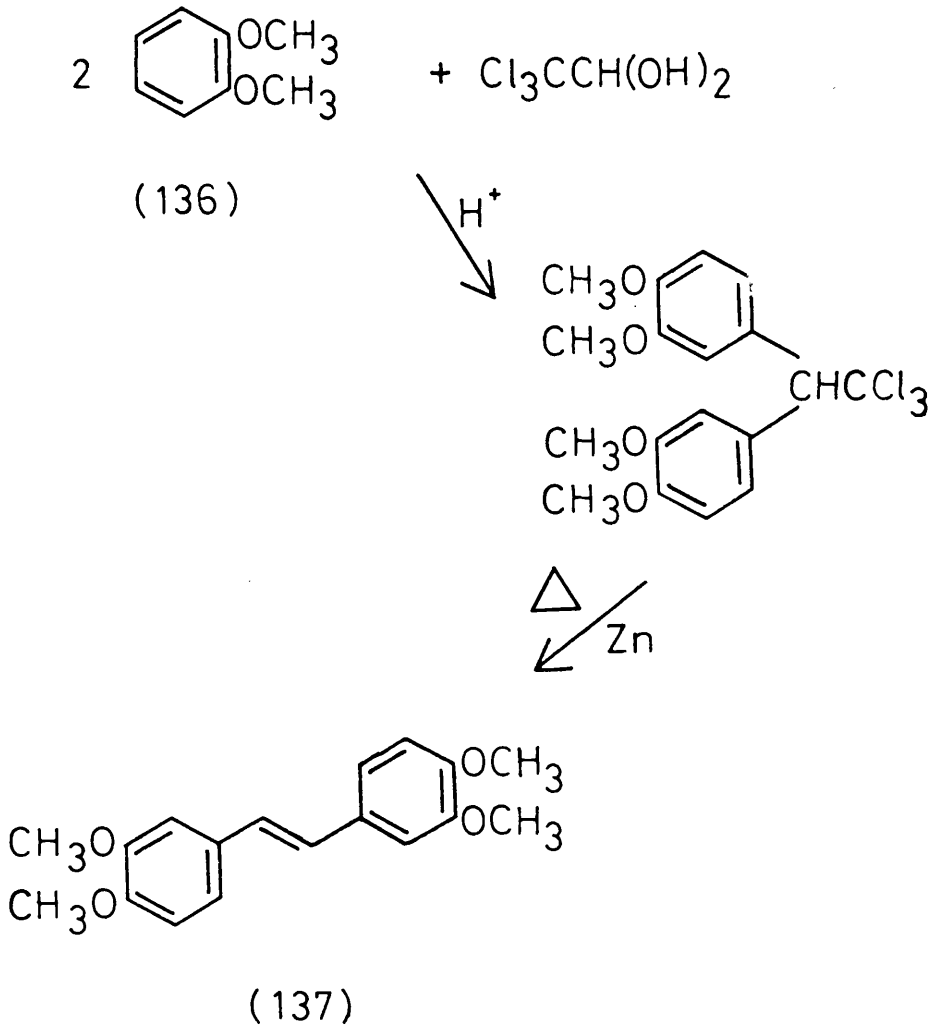
been extravagant and so "superdry" acetonitrile was prepared and "wetted" to the extent of 10^{-2} mol.dm.$^{-3}$ with deuterium oxide. As usual anhydrous sodium perchlorate was the supporting electrolyte.

Preparation of the Electrolyte

The acetonitrile usually used for electrochemical oxidations is distilled from phosphorus pentoxide and contains trace amounts of water; for this work "superdry" acetonitrile was prepared by distilling the solvent twice from phosphorus pentoxide onto activated molecular sieves. The water content after this treatment is reported to be less than 1 ppm .

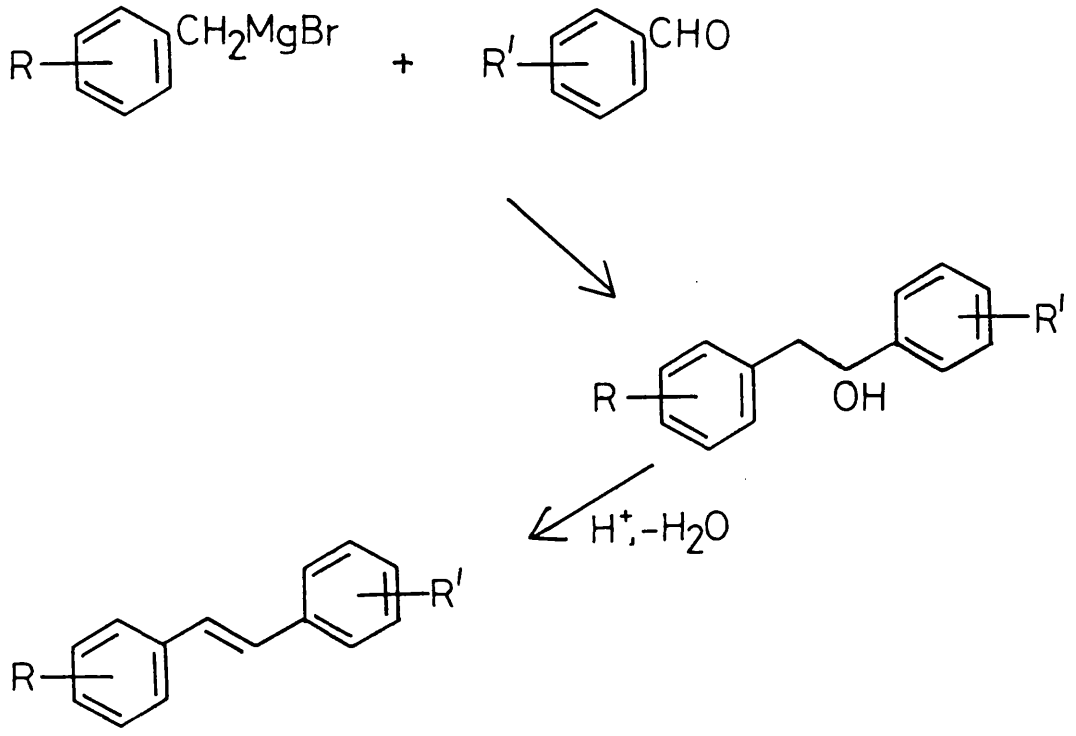
Preparation of 3,3',4,4'-Tetramethoxybibenzyl (1)

Although the classical route to bibenzyl (1) is the treatment of veratrole (136) with chloral hydrate followed by heating with zinc to give the stilbene (137) which can be catalytically reduced to the bibenzyl (1)[4], in our hands this approach was unsatisfactory and the yield of product was only 3%. After three attempts we decided that rather than invest valuable time investigating this problem we should seek alternative syntheses.

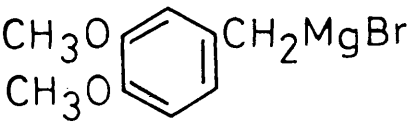


A more general synthesis of stilbenes is the reaction of a benzyl magnesium bromide with an aromatic aldehyde to give an alcohol, followed by dehydration of the alcohol to the stilbene (scheme 13).

Scheme 13

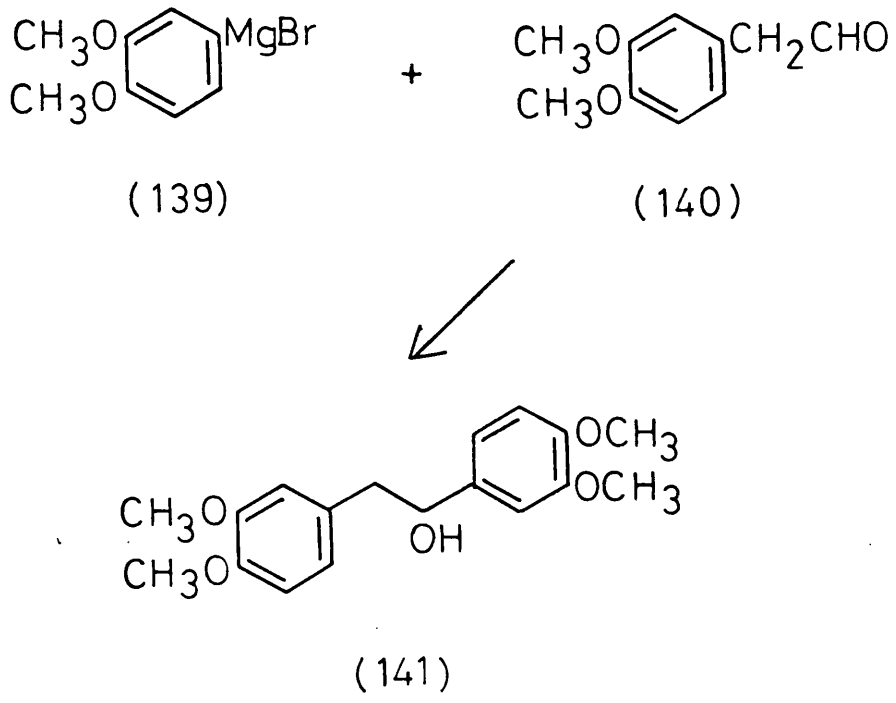


This method cannot be applied to the required stilbene (137) since all attempts to prepare 3,4-dimethoxybenzylmagnesium bromide (138) have been unsuccessful and lead to dehydrodimers and trimers.



(138)

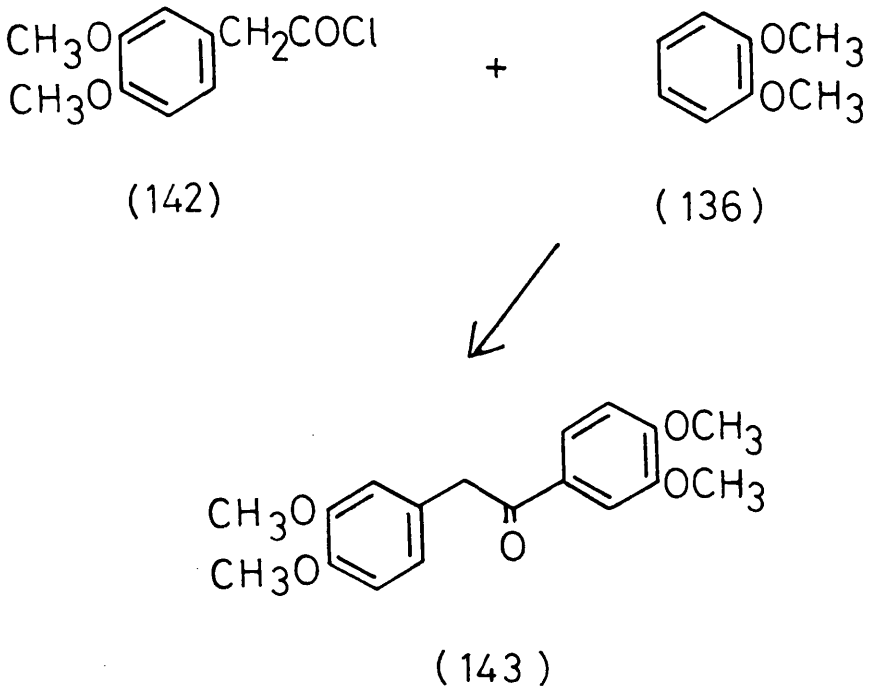
Another possible synthetic route to stilbene (137) is the reaction of 3,4-dimethoxyphenylmagnesium bromide (139) with 3,4-dimethoxyphenylacetaldehyde (140). However, this aldehyde (140) is expensive and the route was not investigated for this reason.



(139) (140)

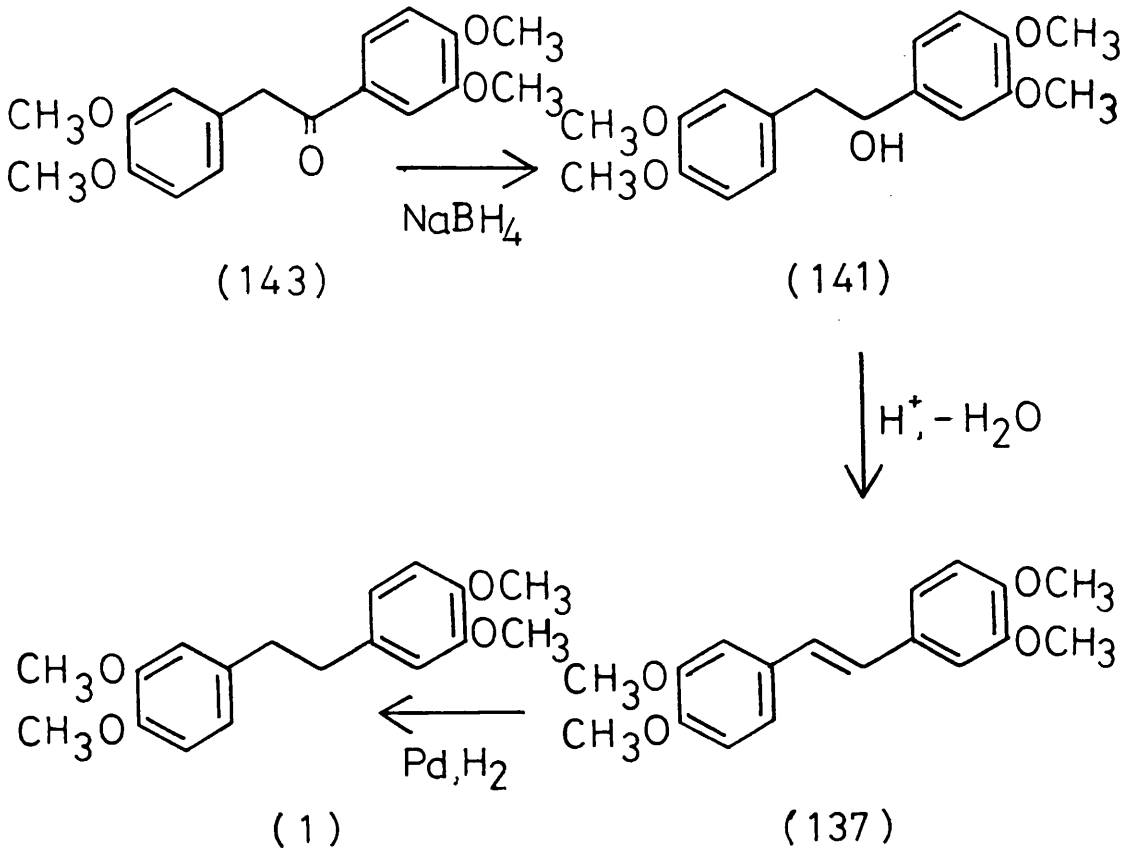
(141)

A more attractive route to bibenzyl (1) is the reduction of 3,3',4,4'-dimethoxydeoxybenzoin (143) which is prepared by Friedel-Crafts acylation of veratrole (136) with 3,4-dimethoxyphenylacetyl chloride (142)[5].



(142) (136) (143)

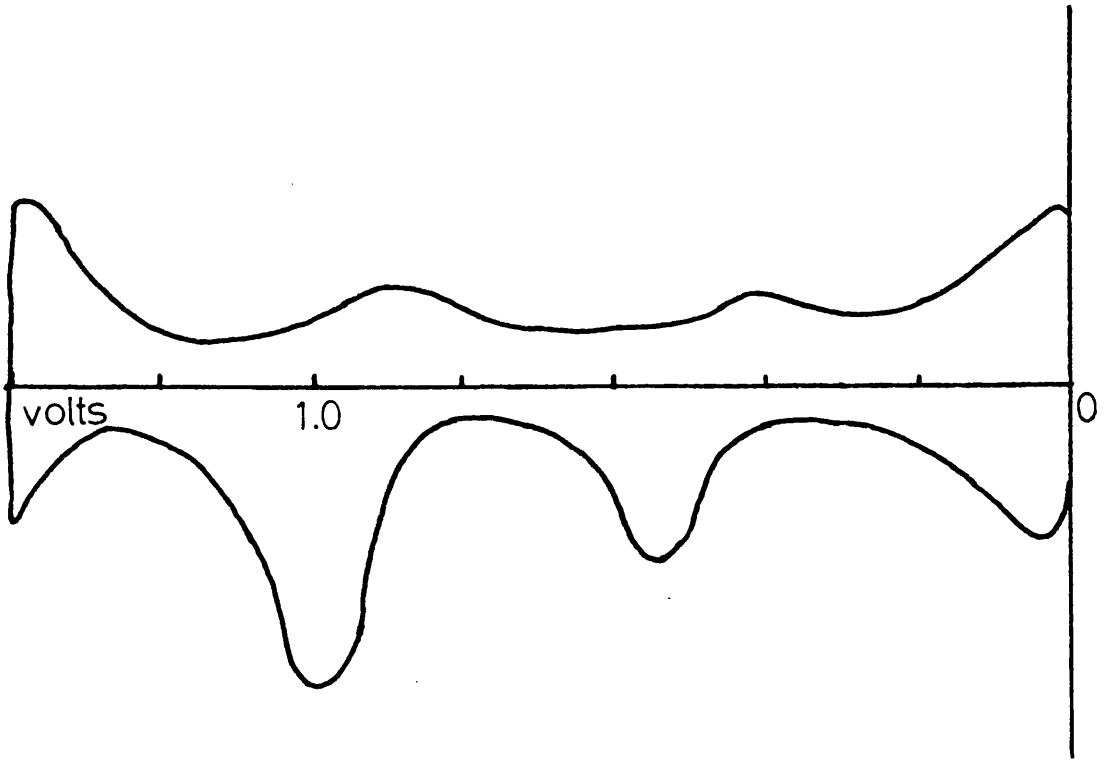
Direct reduction of (143) to bibenzyl (1) by a Wolff-Kishner reaction[6] was unsuccessful and so the stilbene (137) was prepared by reduction of the ketone (143) to the alcohol (141), followed by dehydration[7]. The stilbene (137) was then reduced catalytically to give the required bibenzyl (1).



The cyclic voltammogram (figure 10) of bibenzyl (1) shows an oxidation peak at + 0.95 volts corresponding to the initial ionisation which leads to the dihydrophenanthrene (2). On subsequent sweeps a secondary oxidation peak is observed at + 0.55 volts corresponding to oxidation to the phenanthrene (3).

Figure 10

Cyclic Voltammogram of 3,3',4,4'-Tetramethoxybibenzyl (1)



Anodic Oxidation of 3,3',4,4'-Tetramethoxybibenzyl (1)

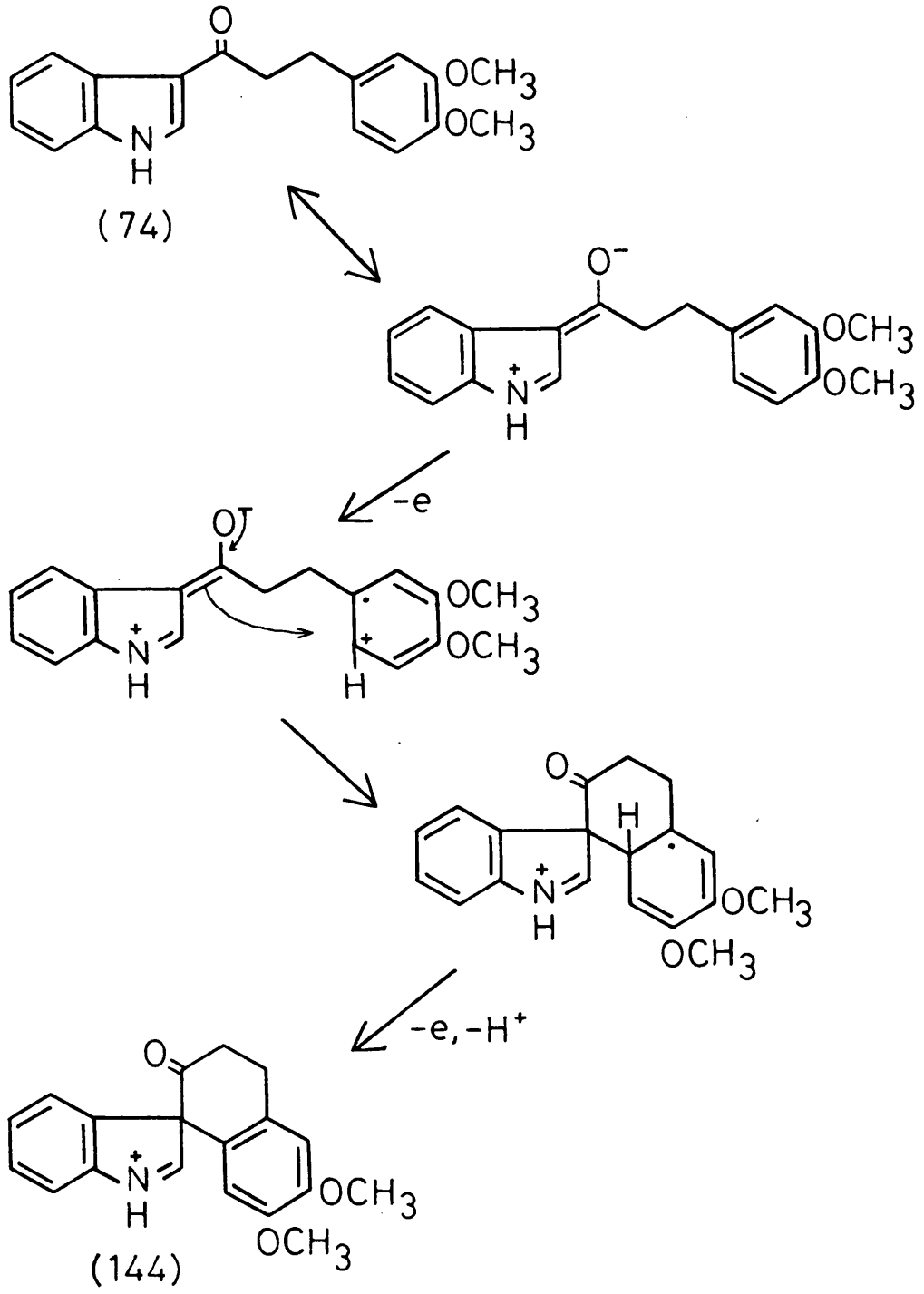
The bibenzyl (1) was electrolysed in 0.1 M sodium perchlorate in dry acetonitrile. Work-up of the anolyte gave the phenanthrene (3) together with unchanged substrate (1). The electrolysis was then repeated in the deuterium-containing electrolyte and worked-up in the usual way. The mass spectrum of the products was identical to that of the products for the normal solvent system and there was no evidence for the incorporation of deuterium atoms in the product (3).

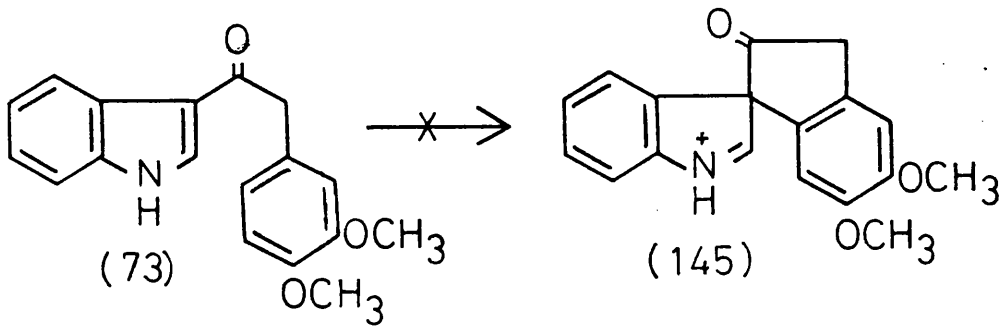
From this it was concluded that the "benzylic cation" mechanism (scheme 12) does not apply to the anodic oxidation of 3,3',4,4'-tetramethoxybibenzyl (1).

Chemical and Electrochemical Oxidation of Indoles

The starting point for our work on indoles was the anodic oxidation of 3-(3,4-dimethoxyphenylpropanoyl) indole (74). It had originally been assumed[8] that the oxidation product was the quinone (76), but qualitative chemical tests cast doubt upon the proposed structure[9]. Difficulties were experienced in handling this compound since it was found to be light sensitive, and it could not be purified by column chromatography. The initial step in the oxidation mechanism is ionisation of the dimethoxyphenyl ring to form a radical cation. This then attacks the indole ring at the 3-position forming a six-membered ring in the spiro-intermediate (144). It was noted[10] that the lower homologue (73) of (74) fails to undergo an intramolecular anodic coupling reaction. These results may be explained by application of the "Baldwin Rules". [11] Formation of (144) is a favoured 6-Endo-Trig process, whereas formation of the five-membered ring in spiro-intermediate (145) is a 5-Endo-Trig process and is disfavoured. The Baldwin Rules are now regarded merely as guidelines because many examples have been recorded of the occurrence of disfavoured reactions. However, the "Rules" do serve here to offer an explanation for the differing electrochemical reactivities of these two indole derivatives which are very difficult to interpret by other means.

The spiro-intermediate (144) may now rearrange in one of two ways, but the cation (146) leading to quinone (76), formed by cleavage

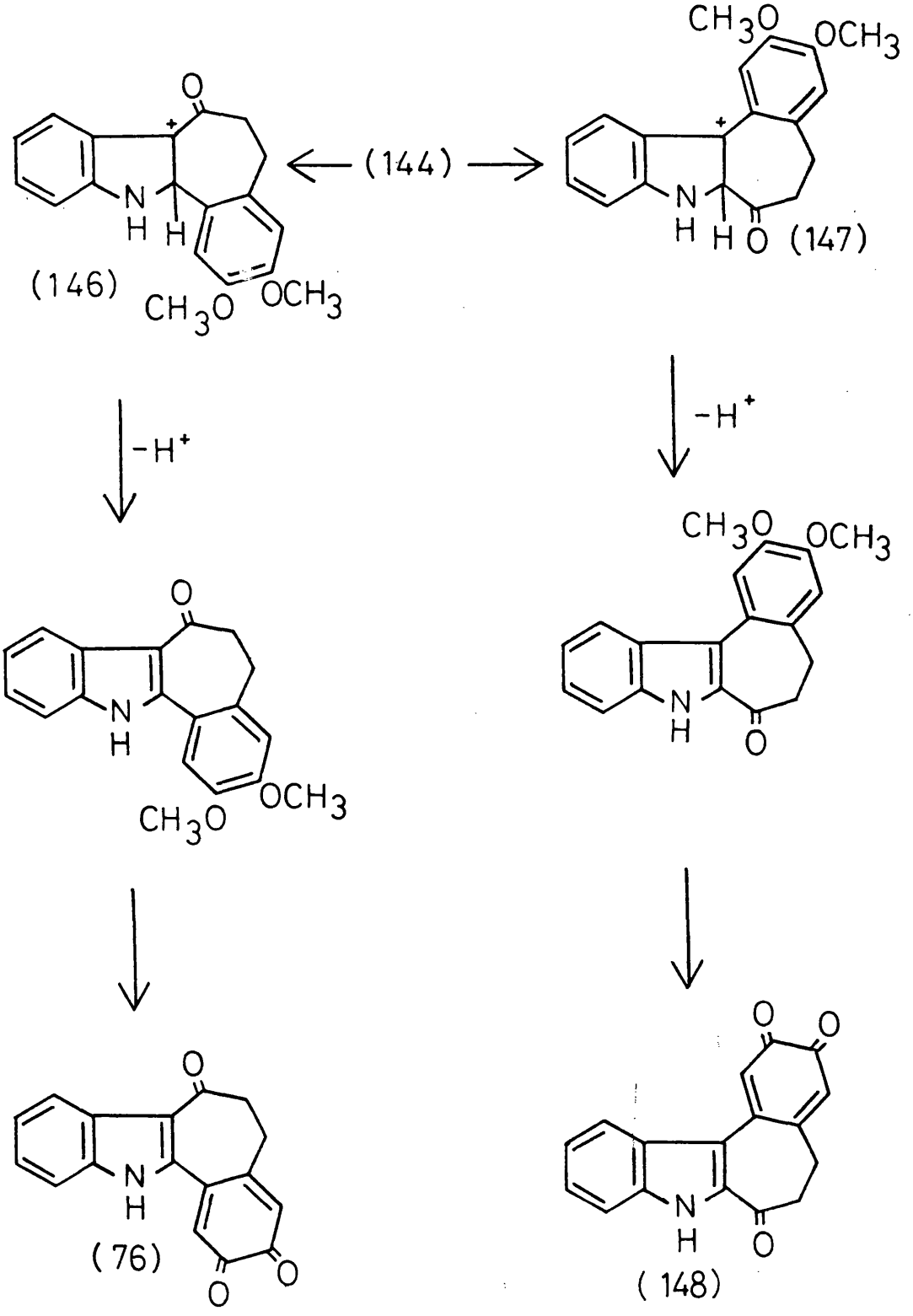

O
OCH3
OCH3
N
H
(74)
O⁻
-e
H
-e,-H⁺
(144)



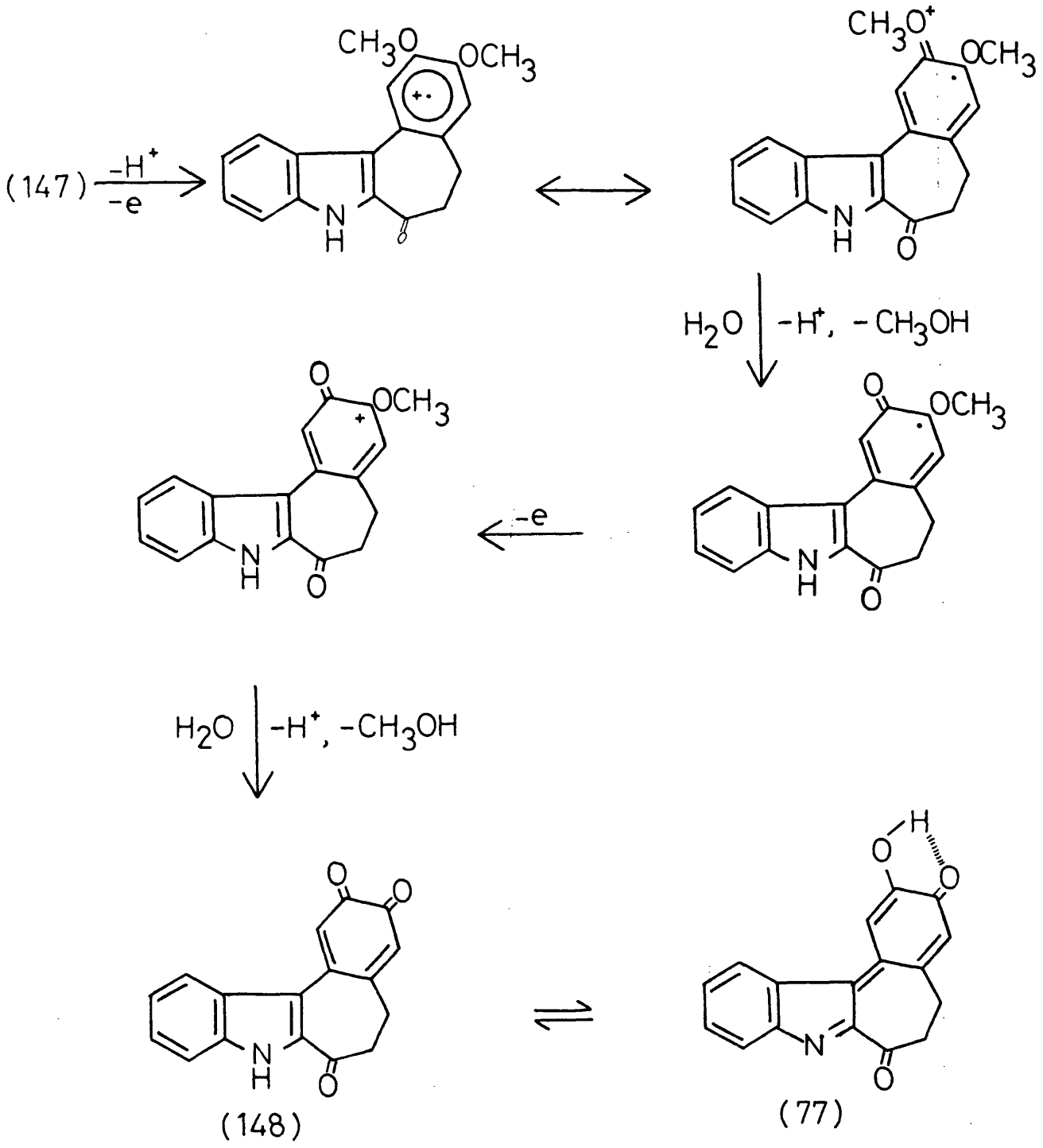
of the bond exocyclic to the dimethoxyphenyl ring is less likely than the alternative ion (147) since it involves a developing positive charge adjacent to a carbonyl group. Thus rearrangement of (144) by migration of the carbonyl group would seem to be the more favoured process, and this would eventually lead to quinone (148) by further oxidation.

The formation of the quinone from the dimethoxyphenyl ring is assumed to be another electrochemical process (scheme 14). (In the reaction 4 Faradays of charge per molecular equivalent of substrate (74) are consumed.) A radical cation is again formed from the dimethoxyphenyl ring and this undergoes attack by water with subsequent loss of methanol. Repetition of this process results in the quinone (148). The absence of the quinone structure in the final electrolysis product suggested by the chemical tests is accounted for by tautomerism of (148) to the chelated enol (77). The structure of this final product rests on spectroscopic and analytical data; it is supported by reasoned arguments, but a more stringent proof of identity is needed, thus we set out to repeat these experiments and to effect

other studies which we felt would confirm the earlier conclusions.



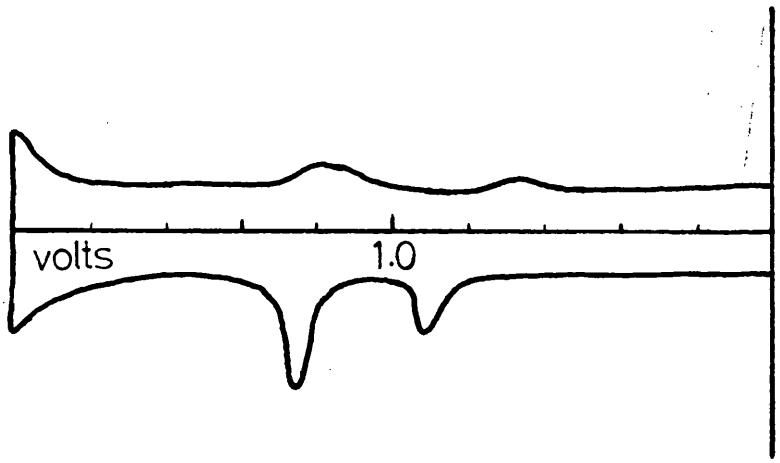
Scheme 14



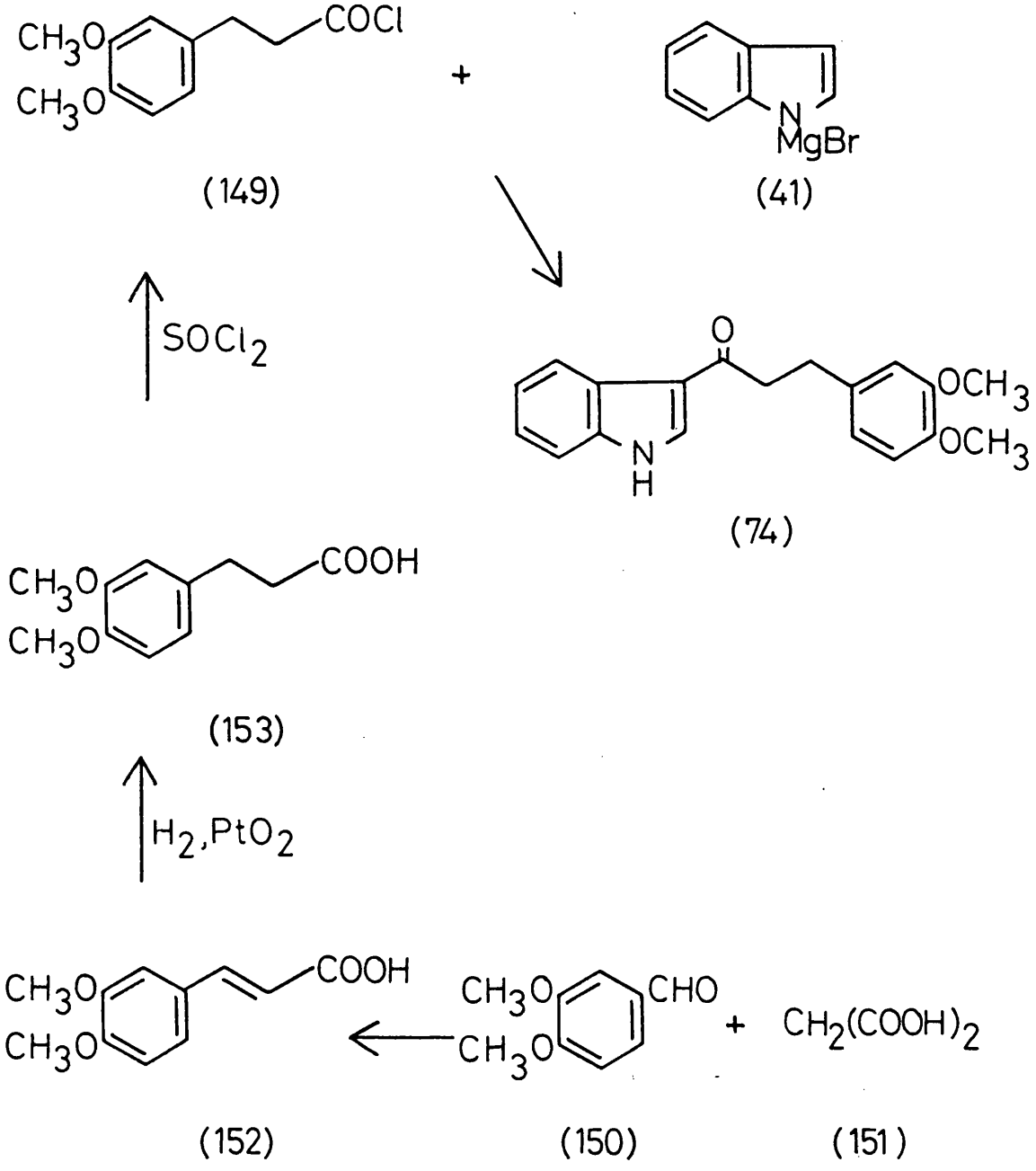
The cyclic voltammogram of (74) shows an initial oxidation peak at + 1.25 volts. On subsequent sweeps a secondary peak is seen at + 0.9 volts corresponding to the oxidative process leading to formation of the quinone (figure 11).

Figure 11

Cyclic Voltammogram of 3-(3,4-Dimethoxyphenylpropanoyl) indole (74)



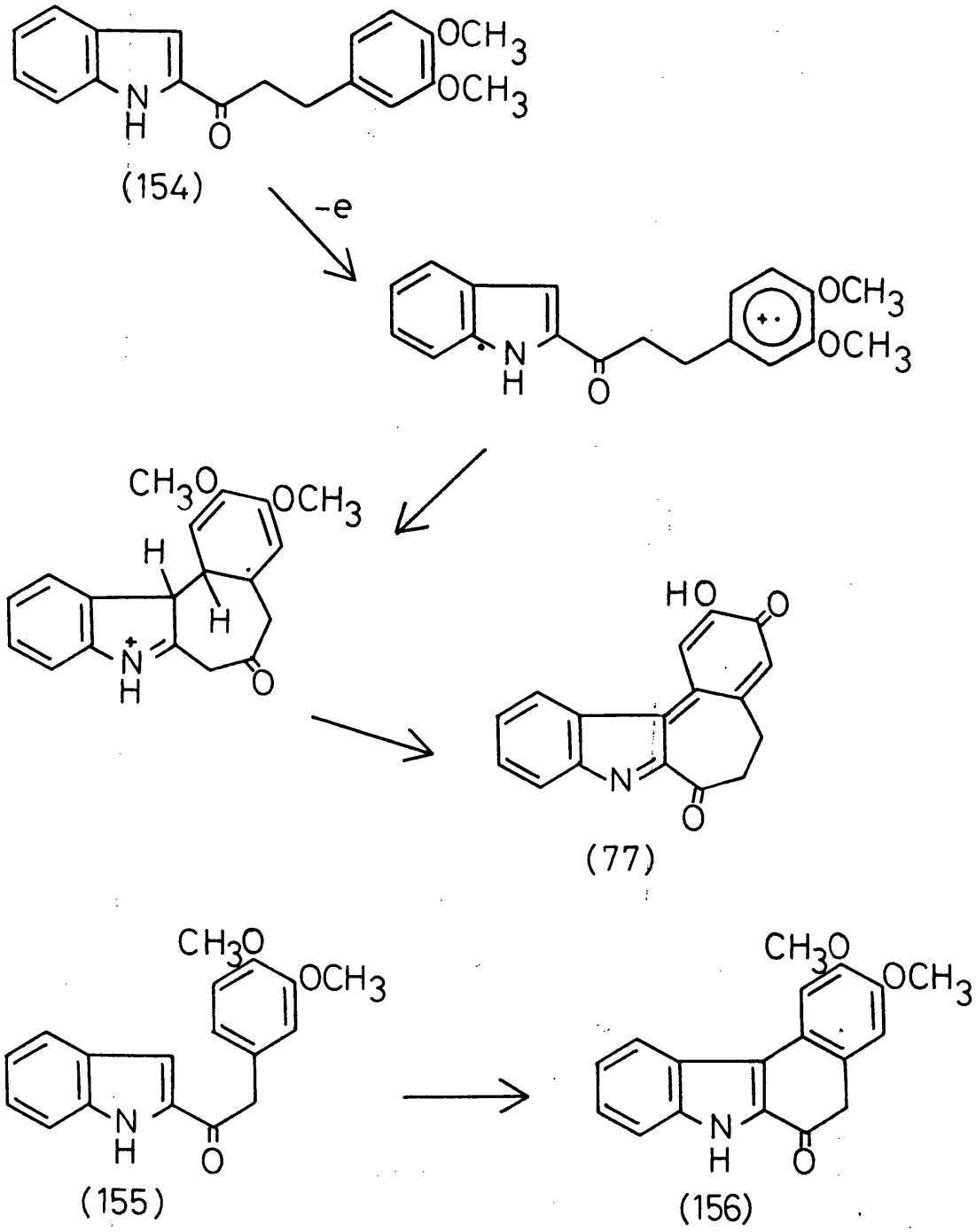
3-(3,4-Dimethoxyphenylpropanoyl) indole (74) was synthesised by the reaction of indole magnesium bromide (41) with 3,4-dimethoxyphenylpropanoyl chloride (149). The condensation of 3,4-dimethoxybenzaldehyde (150) with malonic acid (151) gave rise to 3,4-dimethoxycinnamic acid (152) which was catalytically reduced to 3,4-dimethoxyphenylpropanoic acid (153). Treatment of the acid (153) with thionyl chloride gave the required acid chloride (149).

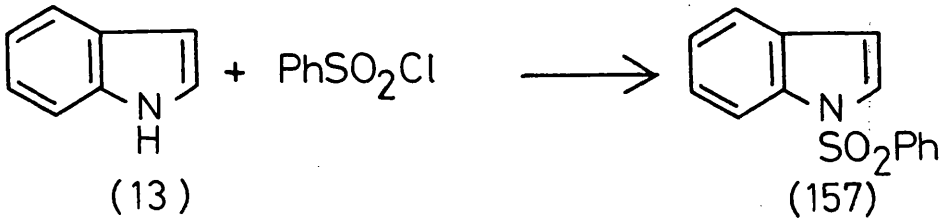

CH3O
CH3O
COCl
+
N
MgBr
(149)
(41)
SOCl2
O
OCH3
OCH3
N
H
(74)
CH3O
CH3O
COOH
(153)
H2,PtO2
CH3O
CH3O
COOH
CH3O
CH3O
CHO
+
CH2(COOH)2
(152)
(150)
(151)

In an attempt to establish the true structure of the oxidation product of (74) the 2-acylindole (154) was synthesised. It was thought that anodic oxidation of this isomer of (74) would give a radical cation which would cyclise directly to the 3-position of the indole ring leading unambiguously to the quinone enol (77) (scheme 15). This reaction would involve a 7-Endo-Trig process which is favoured and it is interesting to note that the homologue (155) of (154) should undergo a favoured 6-Endo-Trig process to give structure (156). A positive result of this kind would provide extra support for our general thesis of the factors that control cyclisations in this area.

The synthesis of 2-(3,4-dimethoxyphenylpropanoyl) indole (154) proved to be unexpectedly difficult and much time was devoted to finding a suitable route to this compound. The first synthetic route tried was the treatment of a 2-lithioindole[12] with acid chloride (149). A suitable protecting group for the indolic nitrogen is benzenesulphonyl[13], the advantage of this group being that it is readily hydrolysed at the end of the reaction sequence under mild conditions[14]. Benzenesulphonylindole (157) was prepared by treatment of indole (13) with benzenesulphonyl chloride in dimethylsulphoxide with potassium hydroxide as base.

Scheme 15


OCH3
OCH3
N
H
O
(154)
-e
OCH3
OCH3
CH3O
OCH3
H
H
N
H
O
HO
O
N
O
(77)
CH3O
OCH3
N
H
O
(155)
CH3O
OCH3
N
H
O
(156)



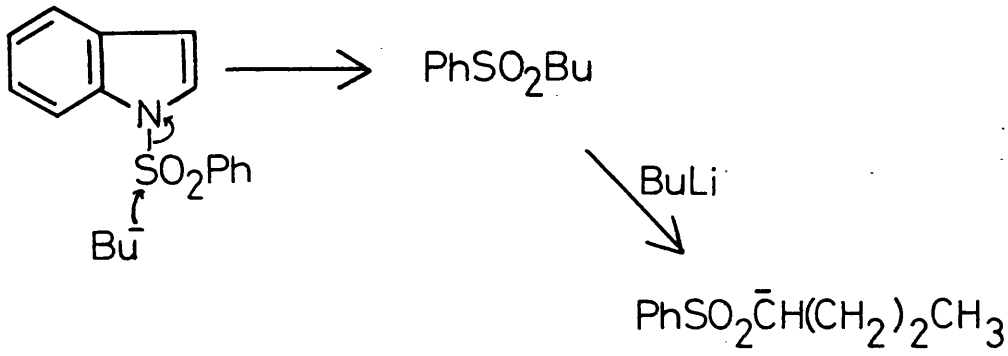
(13) (157)

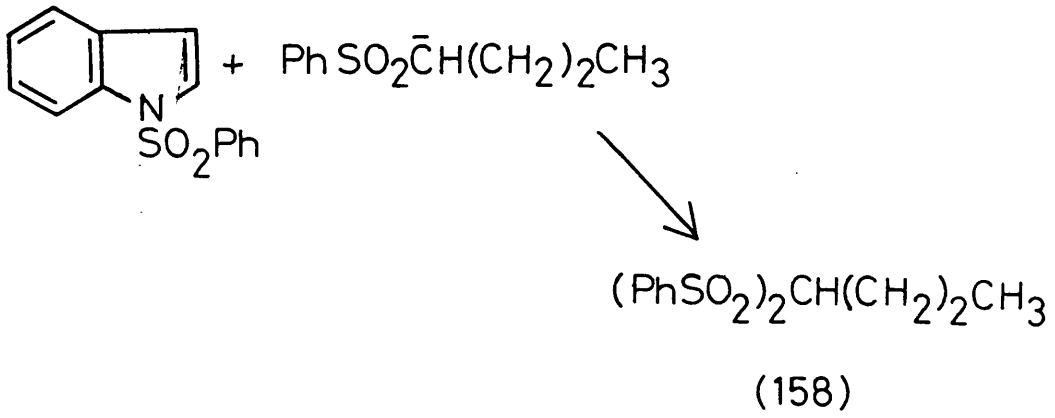
The protected indole (157) was heated under reflux for seven hours with n-butyllithium[12] and to it was added the acid chloride (149). On work-up a gum was obtained. Trituration of the gum with methanol gave a small amount (20%) of a crystalline compound which proved to be 1,1-bis(benzenesulphonyl)butane (158). Prolonged heating with butyllithium obviously cleaved the benzenesulphonyl protecting group (scheme 16). Further work-up of the gum failed to yield any other products.

Shirley and Roussel[12] report that it is necessary to heat benzenesulphonylindole (157) under reflux with butyllithium for metalation to occur; however Joule[15] finds that lithiation occurs under far milder conditions. The indole (157) was treated with butyllithium at -78° and reaction was found to be complete on warming to room temperature. 2-Lithiobenzenesulphonylindole (160) was prepared in this fashion and treated with the acid chloride (149), but only an intractable gum was obtained on work-up.

Acid chloride (149) is unstable and is generally used immediately after its preparation without any form of purification. It was thought

Scheme 16

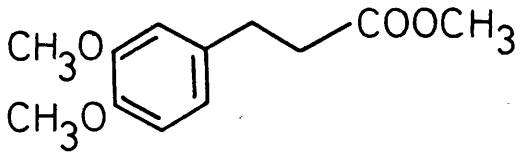




(158)

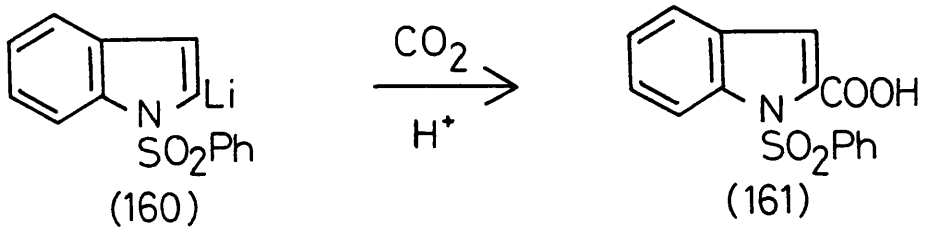
that the failure of the above reaction could be attributable to the poor quality of (149). The chloride (149) was next distilled (b.p. 166° at 0.7 mm Hg) under nitrogen to give a colourless oil which was seen to discolour within a few hours. The reaction with the lithiated indole (160) was repeated using the distilled acid chloride (149) but this also led to a gum. It was thought possible that two molecules of lithiated reagent (160) were reacting with one molecule of acid chloride (149), and so a reverse addition reaction was carried out. The lithioindole (160) was prepared and added to the acid

chloride (149). Again, no product was formed, and in this experiment unreacted starting material (157, 56%) was recovered by column chromatography. In the literature[13] there are many examples of successful preparations of 2-acylindoles by adding acid chlorides to 2-lithioindoles, so reverse addition is obviously not necessary. In these reactions the highest yields are reported using acid chlorides; however, esters can also be used. The methyl ester (159) of 3,4-dimethoxyphenylpropanoic acid (153) is a stable crystalline solid and is consequently much easier to handle than the acid chloride (149).



(159)

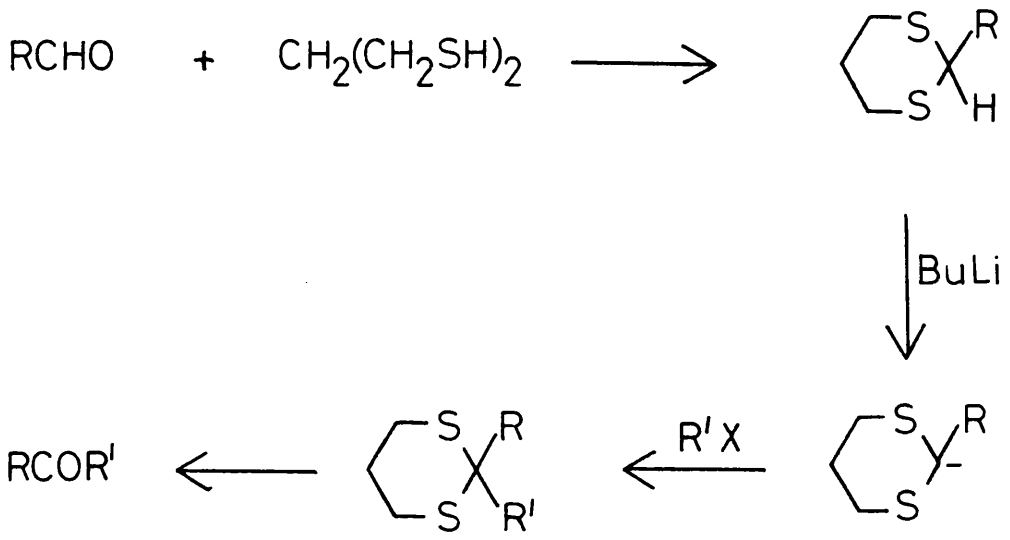
Reaction of the ester (159) with 2-lithiobenzenesulphonylindole (160) failed again to yield any product. It was thought possible that the lithiation procedure could be at fault and so the technique was tested by preparing the lithiated reagent (160) in the usual way and then pouring it onto dry ice. 1-Benzenesulphonylindole-2-carboxylic acid (161) was obtained in 92% yield and this result shows that the lithiation reaction is efficient. Thus the fault in the acylation reaction lies elsewhere.



(160) (161)

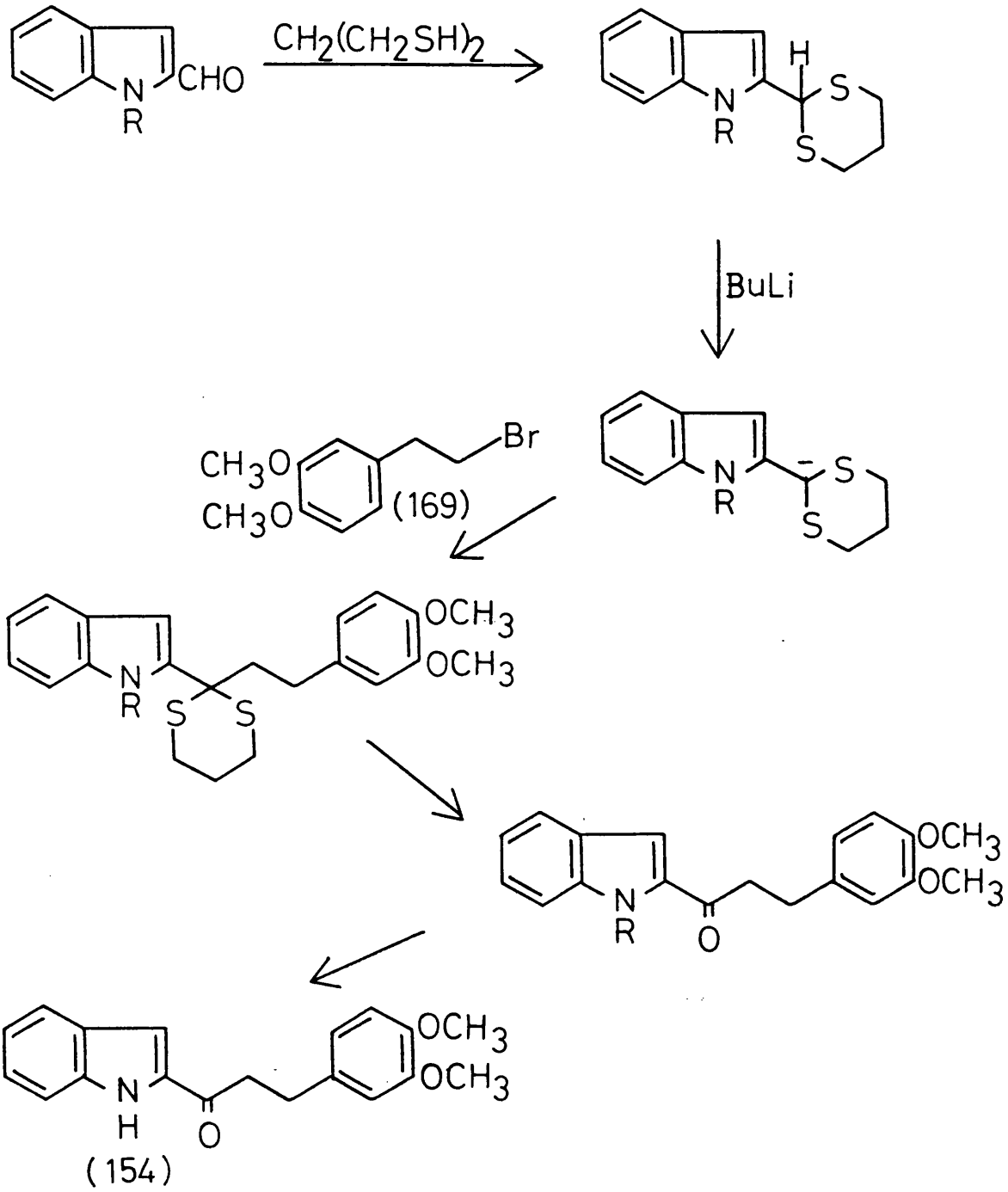
In view of this, direct acylation of 2-lithiobenzenesulphonylindole (160) was abandoned and a new route to the indole (154) was considered. Corey has used thioacetal derivatives of aldehydes in the synthesis of ketones (scheme 17)[16]. The 1,3-dithiane derivative modifies the carbonyl group in such a way that the carbon atom behaves as a nucleophile. Thus the aldehyde proton is rendered acidic by the formation of the cyclic thioacetal by reaction with propane-1,3-dithiol[17]. Treatment of the dithiane with butyllithium followed by alkylation[16] and hydrolysis[18] gives ketones.

Scheme 17



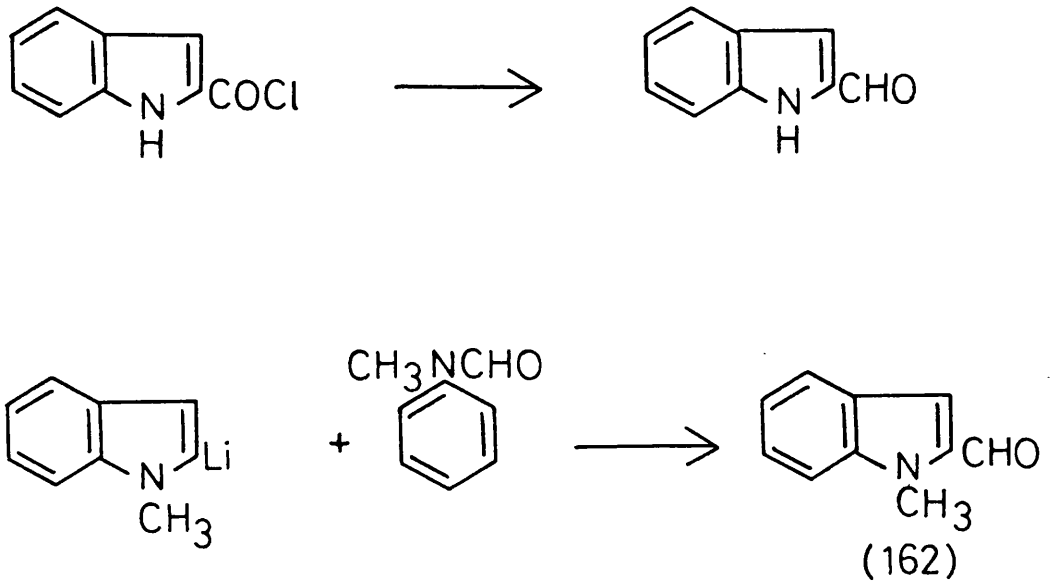
It was proposed that an N-protected indole-2-aldehyde be made and then converted <u>via</u> a dithiane derivative to a 2-acylindole (scheme 18). A suitable protecting group could again be benzenesulphonyl.

Scheme 18



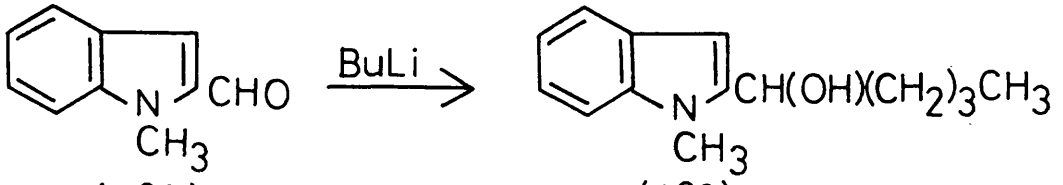
There are two main synthetic routes to indole-2-aldehydes. The first is reduction of an acid chloride (scheme 19)[19], but a better route is the formylation of a 2-lithioindole. Thus, treatment of 1-methyl-2-lithioindole with N-methylformanilide gives 1-methylindole-2-aldehyde (162)[20].

Scheme 19



2-Lithiobenzenesulphonylindole (160) was prepared as before, and treated with N-methylformanilide. In one experiment the reaction mixture was heated under reflux for three hours and in another the mixture was stirred for thirty minutes at room temperature. In both cases work-up gave a dark red intractable tar and none of the desired product was isolated.

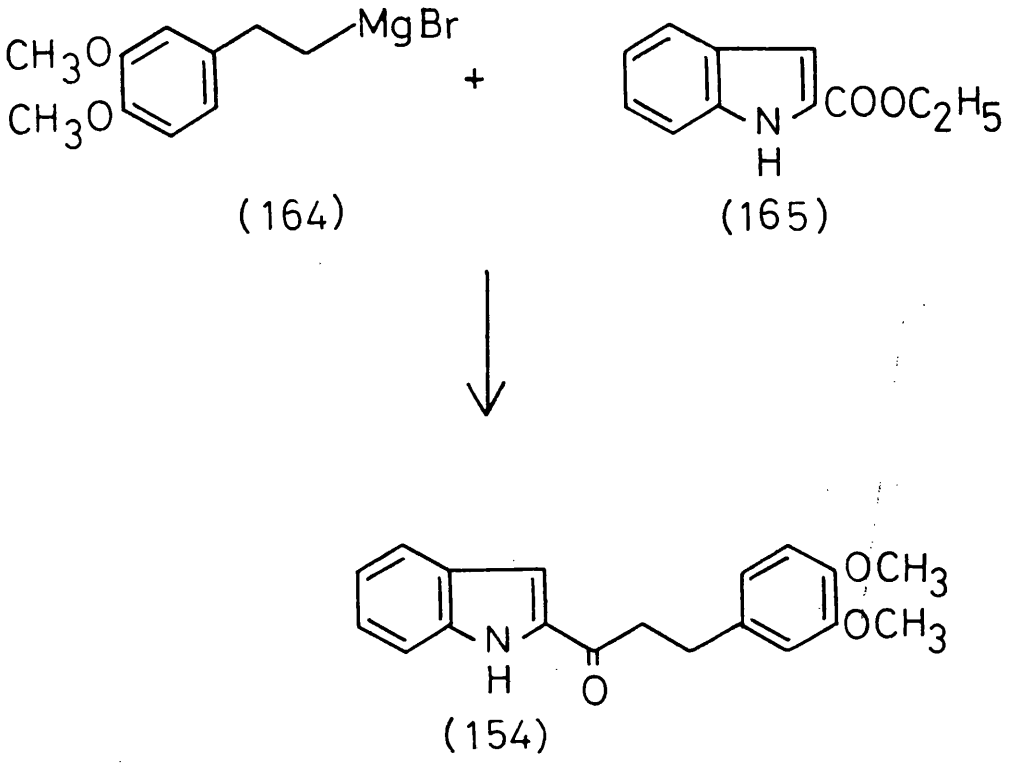
The literature[20] synthesis of 1-methylindole-2-aldehyde (162) was repeated but the yield obtained was only 3%. The patent[20] recommends the use of a 20% excess of butyllithium, but in this experiment the excess butyllithium was found to have reacted with the product (162) giving rise to the pentanol derivative (163). These two products, together with starting material were isolated by column chromatography.



(162) (163)

In view of the fact that the required aldehyde could not be made efficiently in high yield, the dithiane route was put aside.

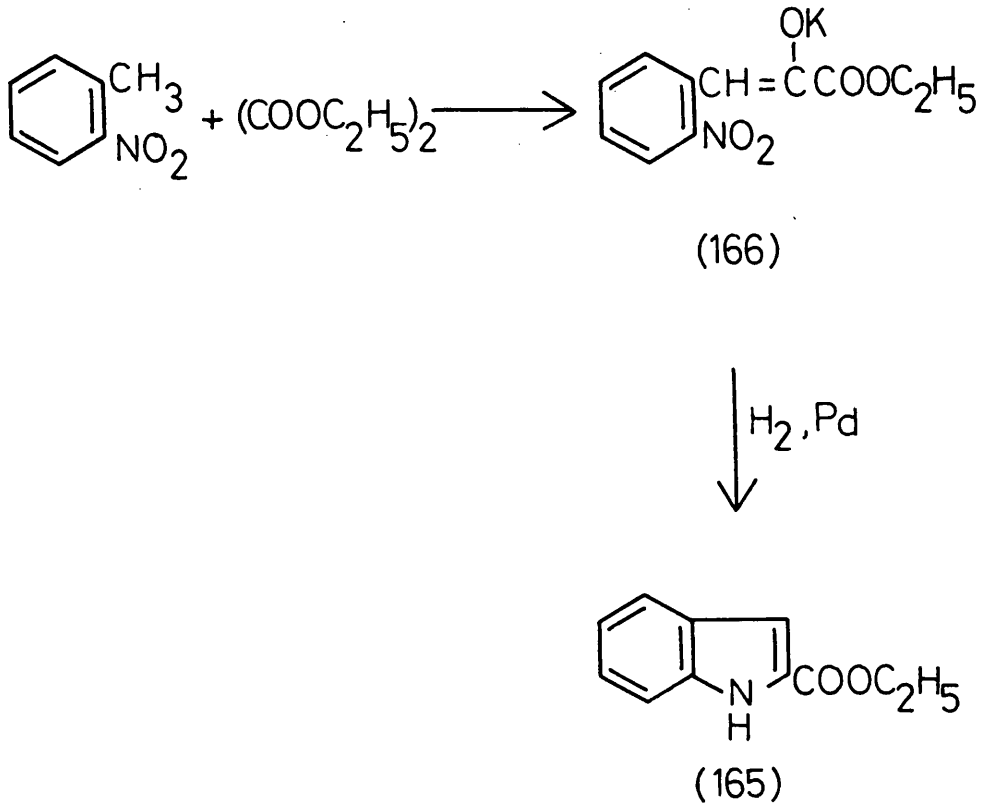
Grignard reagents react with esters to give ketones. The Grignard reagent must be added to the ester and not vice versa to prevent the reaction of two molecules of Grignard reagent with one molecule of ester. It was thought that 3,4-dimethoxyphenethylmagnesium bromide (164) should react with 2-ethoxycarbonylindole (165) to give the required ketone (154).



(164) (165)

(154)

Diethyl oxalate and 2-nitrotoluene were condensed in ethereal potassium ethoxide solution to give potassium ethyl 2-nitrophenyl-pyruvate (166)[21]. This salt undergoes a slow decomposition and so it was catalytically reduced[22] to 2-ethoxycarbonylindole (165) immediately after preparation.

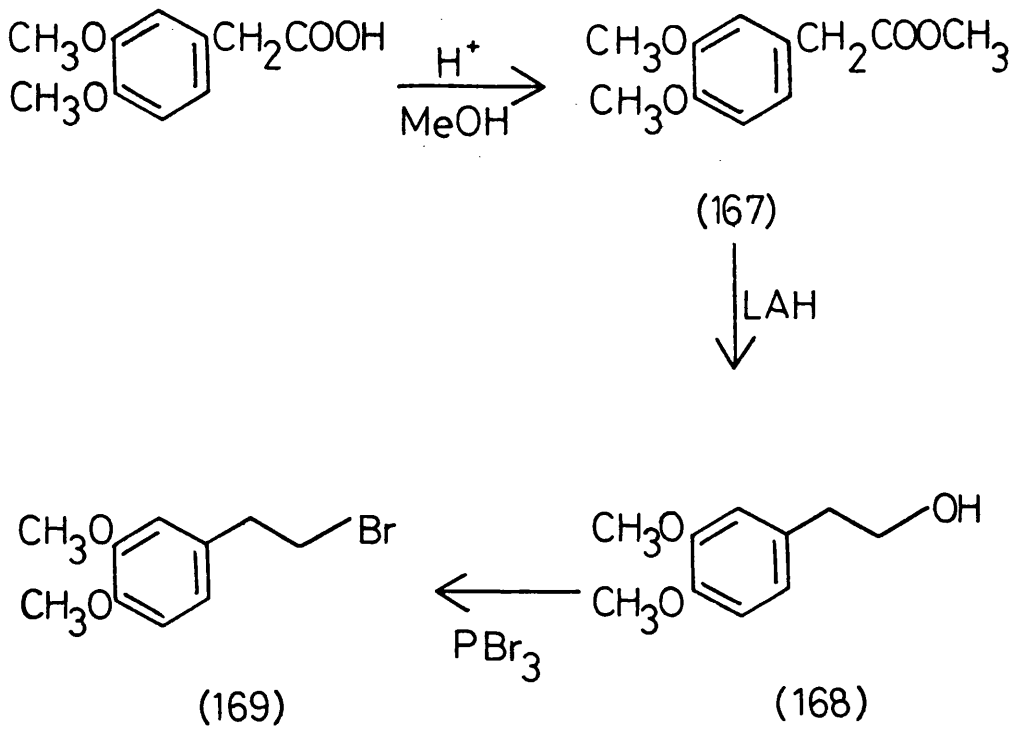


(166)

(165)

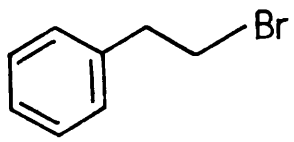
2-(3,4-Dimethoxyphenyl)bromoethane (169) was prepared by reducing methyl 3,4-dimethoxyphenylacetate (167)[23] with lithium aluminium hydride, and then treating the alcohol obtained (168) with phosphorus tribromide[24].

The bromide (169) was added to dry magnesium turnings in ether but no reaction was seen to occur. The magnesium failed to dissolve and (169) was returned unchanged. The reaction was repeated with tetrahydrofuran as solvent but again there was no reaction even on heating under reflux for several hours. Ehrlich and Sachs[25] report

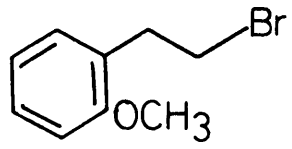


a technique which is of use in initiating some difficult Grignard reactions. The magnesium turnings are activated by the addition of a little bromoethane, then the liquid is decanted and the bromide is added. This method was tried with (169), but again there was no reaction. In all these reactions the magnesium and (169) were returned quantitatively. Great care was taken to ensure that the glassware, solvents and reagents were all scrupulously dry, but this was to no avail.

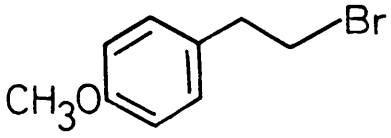
A literature search revealed that the Grignard reagent of 2-phenylbromoethane (170)[26] is known, as are the Grignard reagents prepared from 2-(2-methoxyphenyl)bromoethane (171)[27] and 2-(4-methoxyphenyl)bromoethane (172)[28]. However, there are no references to 2-(3-methoxyphenyl)bromoethane (173) or to 2-(3,4-dimethoxyphenyl)bromoethane (169).



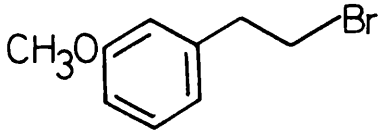
(170)



(171)

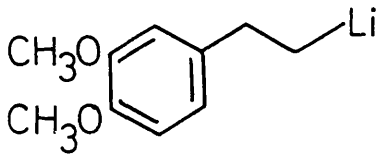


(172)



(173)

We cannot account for this failure and we were reluctant to concede defeat but since the formation of the Grignard reagent (164) proved so difficult, attempts were made to prepare the corresponding lithium reagent (174) for reaction with 2-ethoxycarbonylindole (165).



(174)

No reaction was observed between the bromide (169) and lithium metal. The preparation was repeated using the method of Kaiser and Petty[29] in which butyllithium is reacted with diisopropylamine to form lithium diisopropylamide, a strong metalating agent. This reagent was treated with the bromide (169) and then added to 2-ethoxycarbonylindole (165). On work-up a solid was obtained which was shown by comparative thin layer chromatography to consist solely of the two starting materials (169) and (165).

$$BuLi + (iPr)_2NH \rightarrow LiN(iPr)_2 + BuH \uparrow$$

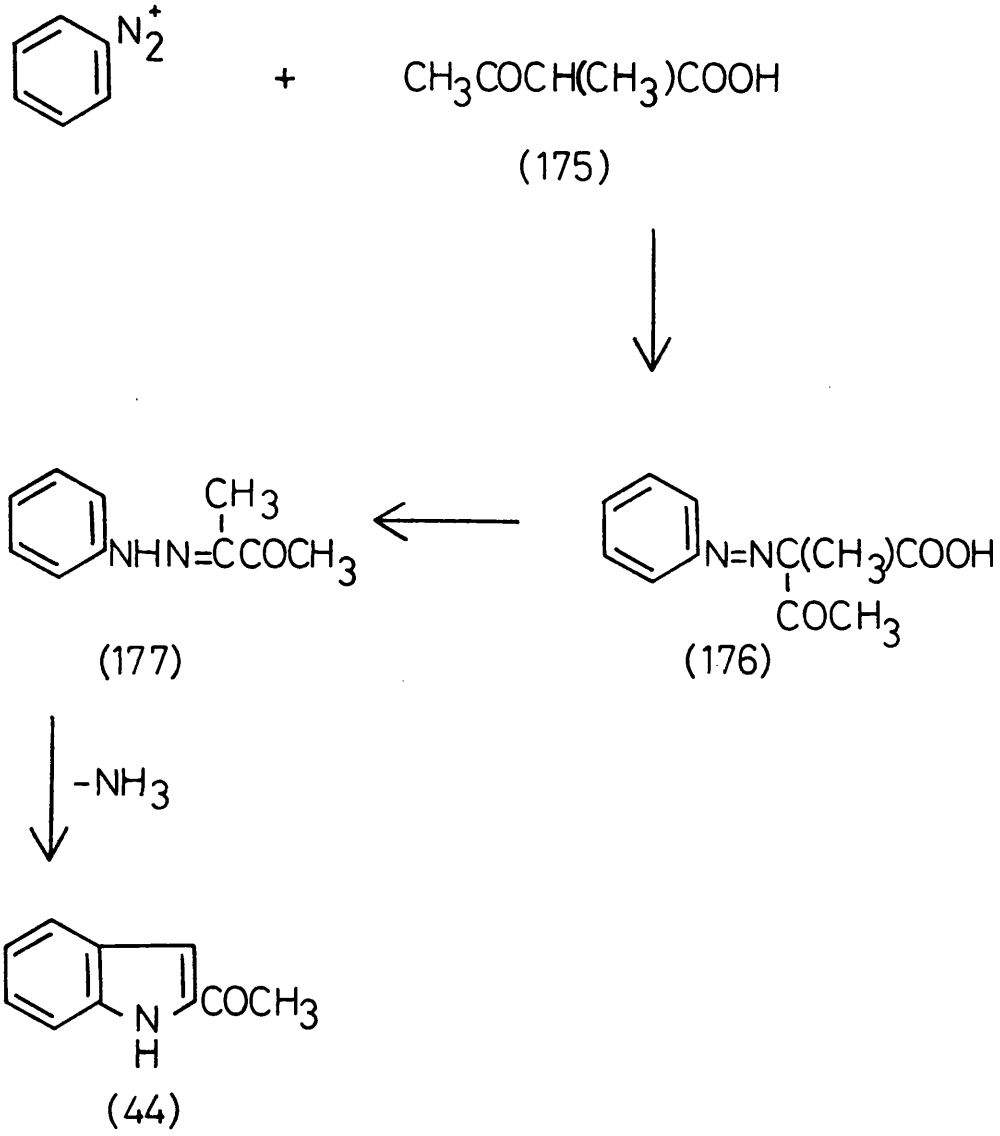
Since neither the Grignard reagent nor the organolithium derivative of 2-(3,4-dimethoxyphenyl)bromoethane (169) could be prepared, this synthetic route to the indole (154) was abandoned.

The best-known classical synthesis of indole derivatives is the Fischer reaction and we began to consider the synthesis of the required 2-acylindole (154) using this method. Before this synthesis was attempted a series of model reactions was carried out to establish the best conditions for the preparation of 2-acylindoles. The model

compound chosen was 2-acetylindole (44). The usual synthesis of this compound[30] by treatment of indole with acetic anhydride in the presence of magnesium perchlorate is probably of no use here since it is reported that it cannot be applied to more complex acyl groups. 2-Acetylindole (44) has been prepared in 47% yield by a Fischer synthesis[31] using a mixture of sulphuric acid and formic acid as the cyclising agent. This yield is obviously too low for the reaction to be of any synthetic value and so a variety of other cyclising agents and conditions were used by us in an attempt to find an efficient synthesis of 2-acetylindole (44) which could then be adapted to the preparation of the 2-acylindole (154). For this work the hydrazone (177) was made in the following way: benzenediazonium chloride was prepared from aniline and treated with 2-methylacetoacetic acid (175) to form the azo compound (176). This compound decarboxylated on treatment with sodium acetate and gave the required compound (177, scheme 20)[32].

The first attempt at cyclisation of the hydrazone (177) to 2-acetylindole (44) was made by heating the substrate in 3N ethanolic hydrochloric acid[33]. This was unsuccessful and the starting material was returned unchanged. Similarly, heating the hydrazone (177) in glacial acetic acid failed to induce cyclisation. A third attempt was made by mixing (177) and polyphosphoric acid[33]. A vigorous exothermic reaction occurred and the temperature rose rapidly to 170°, the result was a charred black tar from which no organic material could be extracted. Chastrette[31] has observed that polyphosphoric acid at 100° effects the rearrangement of 2-acetylindole (44) to 3-acetylindole, so if any product had been formed in the reaction, the elevated temperature would have facilitated rearrangement.

Scheme 20

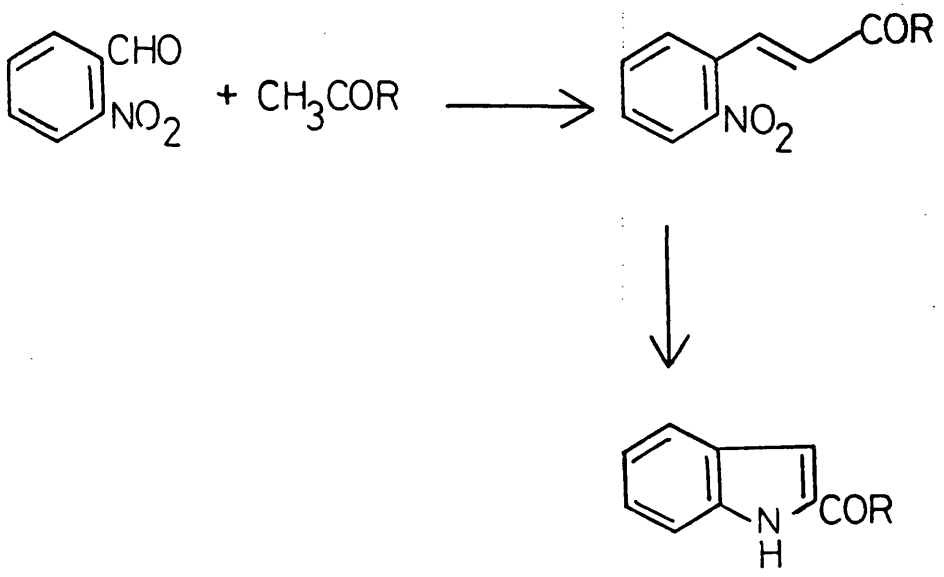

N2+
+
CH3COCH(CH3)COOH
(175)
N=NC(CH3)COOH
COCH3
(176)
NHN=CCOCH3
CH3
(177)
-NH3
N
H
COCH3
(44)

There are examples in the literature of successful Fischer syntheses involving thermal cyclisation by heating in high-boiling solvents such as diethylene glycol[34] and so hydrazone (177) was heated under reflux in diethylene glycol but work-up afforded only the starting material.

The final attempt involved the use of polyphosphoric ester. This reagent offers certain advantages over the use of polyphosphoric acid[35] since it is soluble in chloroform and any heat liberated during a reaction can be dissipated throughout the solvent thus preventing charring. The ester is prepared by heating phosphorus pentoxide under reflux with dry ether in chloroform. The ester is then used as a solution in chloroform. Treatment of the hydrazone (177) with polyphosphoric ester again failed to induce cyclisation and the substrate was returned unchanged. From these results it does not seem possible to find an efficient Fischer synthesis of 2-acetylindole (44) and there seemed to be little point in attempting to extend the reaction to a more complex derivative.

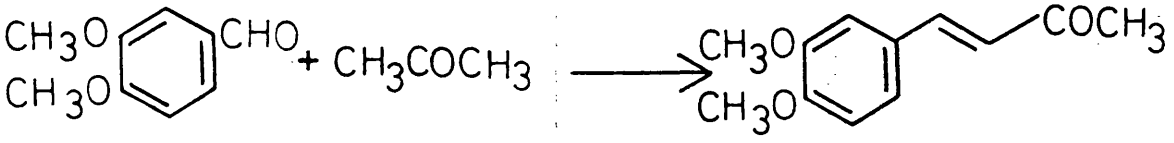
Pyrolysis of 2-azidostyrenes[36] and triethylphosphite reduction of 2-nitrostyrenes[37] are both cyclisation reactions which give rise to indoles. Both involve the generation of a nitrene as intermediate. In preference to handling potentially explosive azides the synthesis of a suitable 2-nitrostyrene derivative was attempted; thus treatment of 2-nitrobenzaldehyde with a methyl ketone should give a styrene which is suitable for cyclisation to a 2-acylindole (scheme 21).

Scheme 21



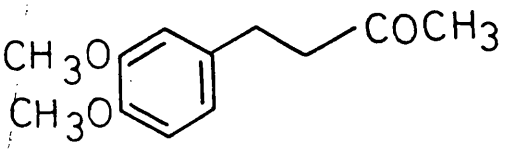
The saturated ketone (180) would be of no use in this synthetic route since condensation with 2-nitrobenzaldehyde would occur at the methylene function adjacent to the carbonyl group. To ensure reaction at the terminal methyl group, the unsaturated derivative (179) was prepared. The unwanted double bond can be reduced out at a later stage in the synthesis. This ketone (179) was prepared by condensation of 3,4-dimethoxybenzaldehyde (178) with acetone[38].

Unfortunately all attempts to condense ketone (179) with 2-nitrobenzaldehyde were unsuccessful. The ketone was treated with the aldehyde in the presence of sodium hydroxide in water and ethanol[39], but the product was an inseparable black tar. The condensation was tried again keeping the temperature below 25° and this time a red oil



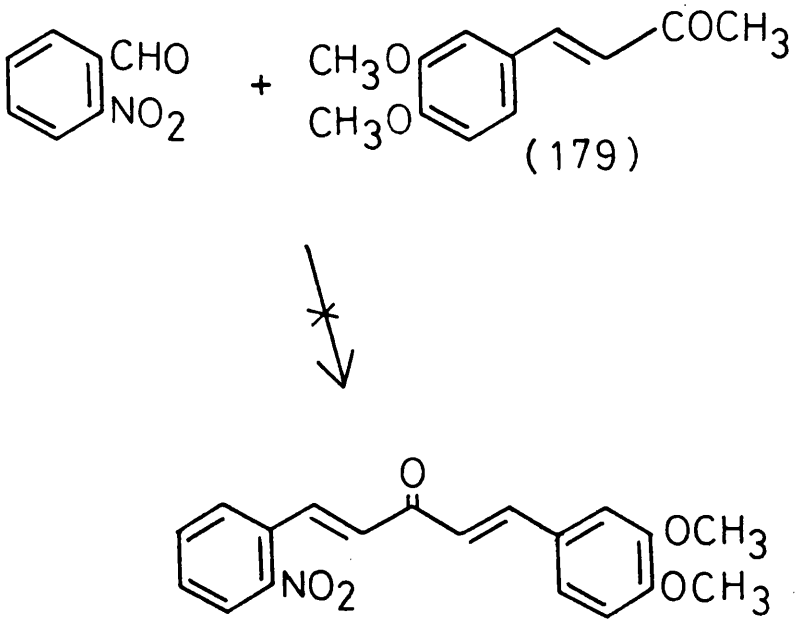
(178)

(179)



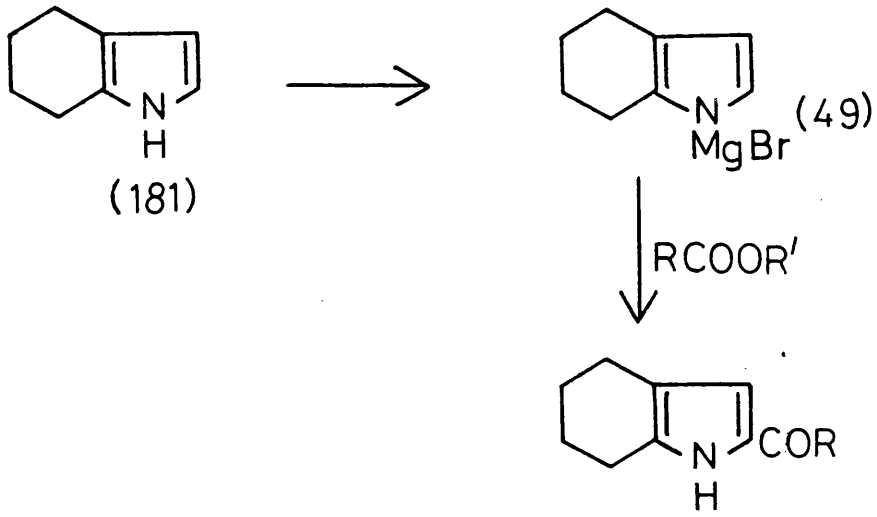
(180)

was obtained on work-up, but this could not be purified even by column chromatography. A final attempt at this condensation was made under non-aqueous basic conditions. The two reactants were heated with piperidine, but no condensation occurred and the starting materials were returned unchanged.

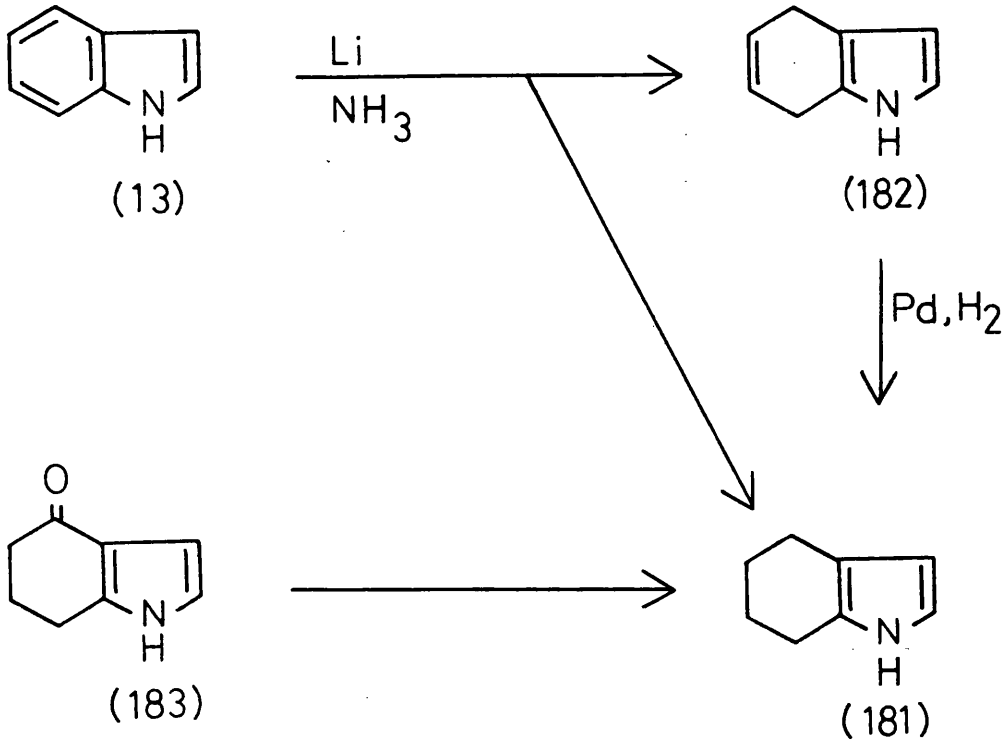


The final synthetic approach to 2-(3,4-dimethoxyphenylpropanoyl)-indole (154) proved to be successful. Joule[15] has made use of the fact that 4,5,6,7-tetrahydroindole (181) behaves not as a normal indole, but as a dialkylpyrrole and is thus subject to electrophilic attack at the 2-position rather than at the 3-position. Thus 4,5,6,7-tetrahydroindole magnesium bromide (49) when added to esters gives 2-acyl-4,5,6,7-tetrahydroindoles. The use of esters rather than acid chlorides is an important advantage of this synthetic method, particularly in view of the difficulties experienced in the use of the

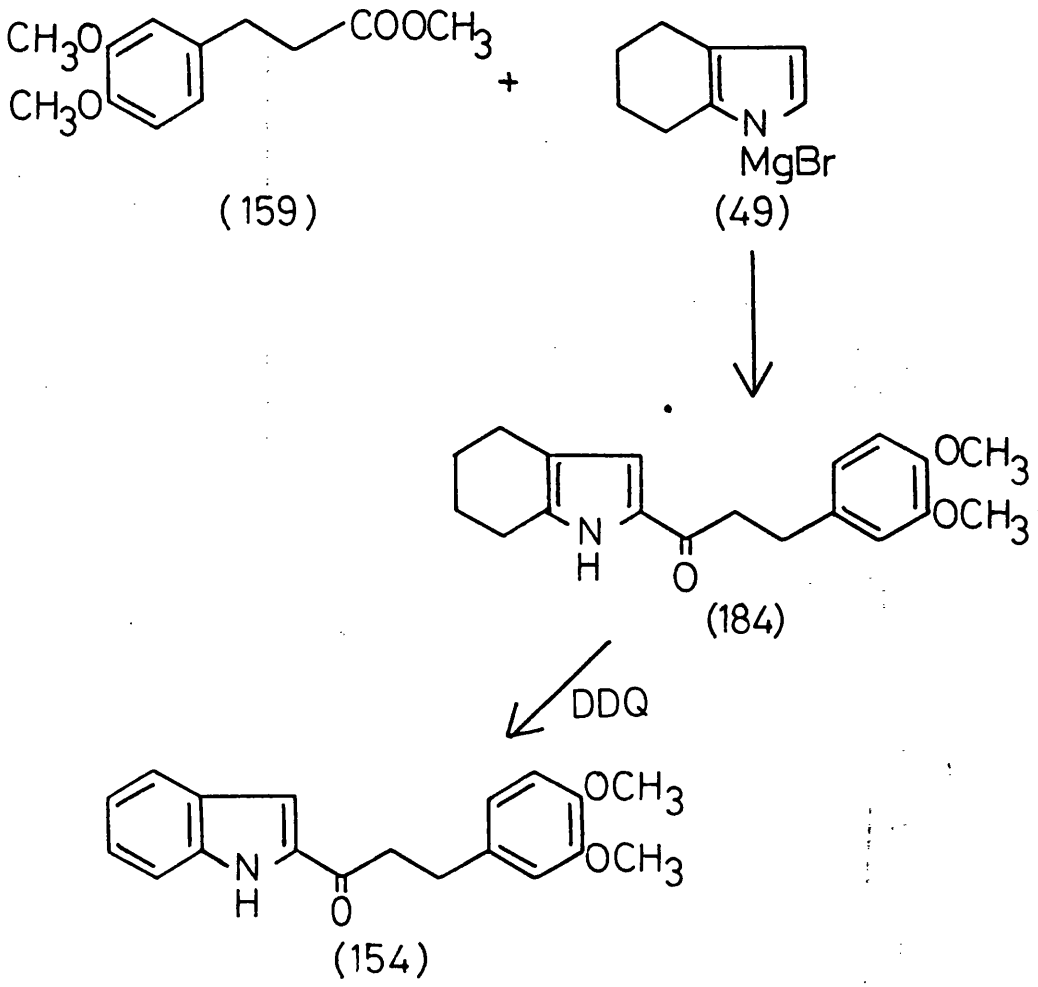
unstable 3,4-dimethoxyphenylpropanoyl chloride (149).



Until recently tetrahydroindole (181) was prepared by the Wolff-Kishner reduction of 4-oxo-4,5,6,7-tetrahydroindole (183)[40], but the Birch reduction of indole (13) with lithium in liquid ammonia gives a mixture of (181) and 4,7-dihydroindole (182)[41], and Joule[15] has found that catalytic reduction of this mixture then gives tetrahydroindole (181) as the sole product.



Tetrahydroindole (181) was prepared in this way and then converted to the Grignard reagent (49). This was added to methyl 3,4-dimethoxyphenylpropanoate (159) to give 2-(3,4-dimethoxyphenylpropanoyl)-4,5,6,7-tetrahydroindole (184). The preferred agent for the oxidation of (184) back to the parent indole (154) was 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[42]. This route provided the required indole (154) albeit in moderate yield.

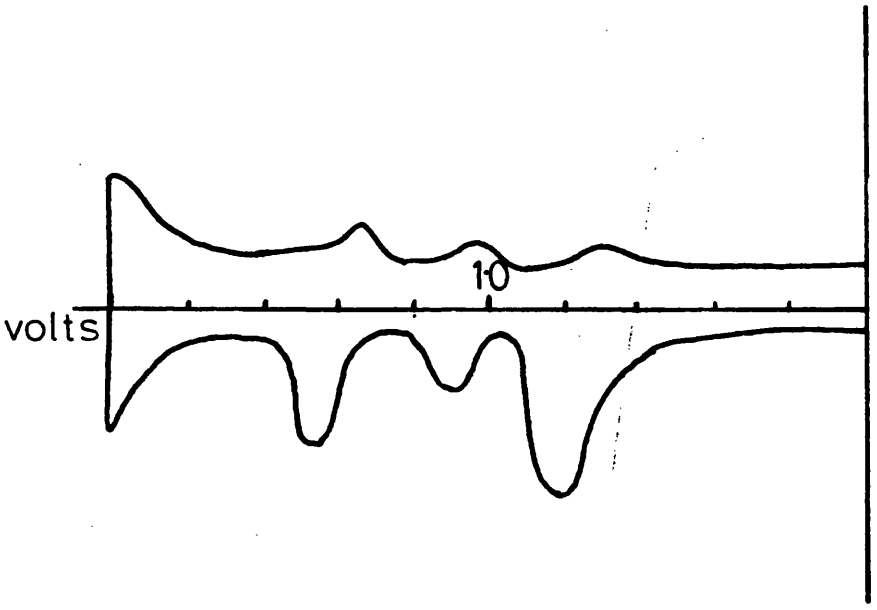


The cyclic voltammogram (figure 12) of 2-(3,4-dimethoxyphenyl-propanoyl)indole (154) shows an initial oxidative peak at + 0.8 volts corresponding to oxidation of the nitrogen lone pair of electrons. Additional peaks are observed at + 1.1 and + 1.45 volts corresponding to ionisation of the dimethoxyphenyl and indole rings respectively. Interestingly, the isomeric 3-acylindole (74) does not exhibit a low potential oxidation peak in its cyclic voltammogram (figure 11). This was a rather disturbing observation for it suggested that inter-molecular reactions involving the indole ring might now occur before

the dimethoxyphenyl ring could be brought into play.

Figure 12

Cyclic Voltammogram of 2-(3,4-Dimethoxyphenylpropanoyl)indole (154)



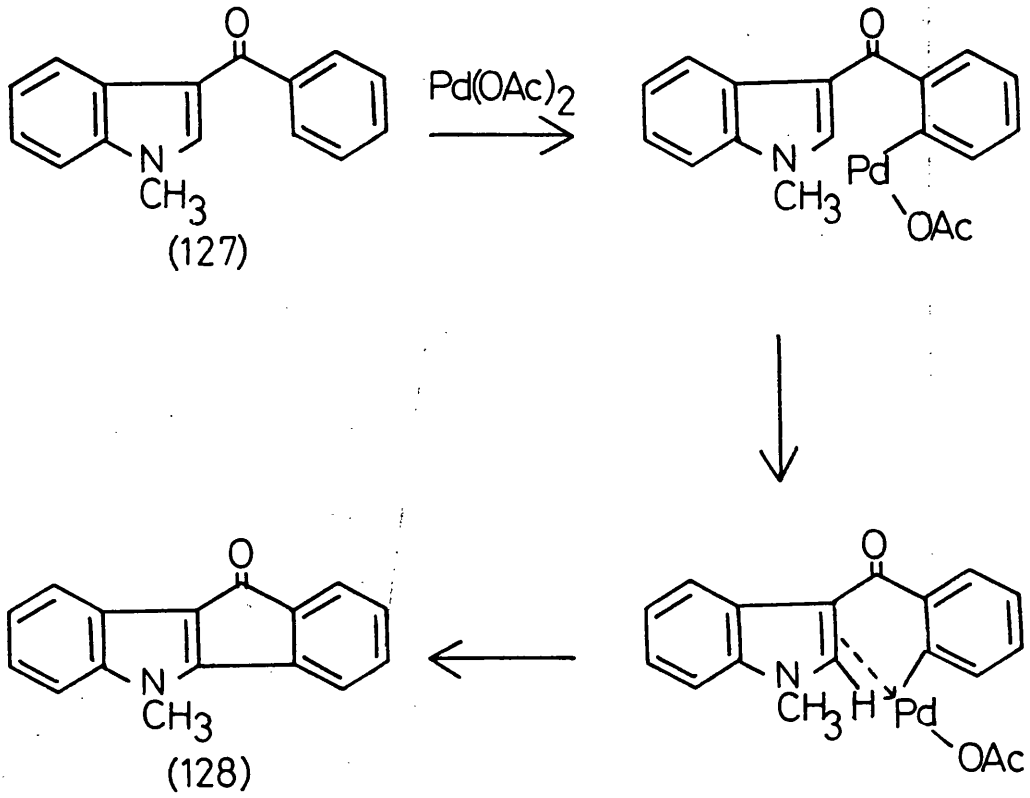
Indeed when the compound (154) was electrolysed at a potential of + 1.2 volts, $3F.mol^{-1}$ of charge was consumed and work-up only gave a tarry solid from which starting material (10%) was returned. No other products were isolated. The electrolysis was then repeated at + 0.8 volts but again only tar and starting material were obtained. In both these experiments the mass spectrum of the product prior to chromatography showed a peak at $^{m}/_{e}$ 210 possibly due to 3,4-dimethoxyphenylpropanoic acid (153) although this compound was not isolated and in support of this Miller[43] reports the formation of carboxylic acids by fragmentation of ketones in electrochemical oxidations. It had been hoped that the oxidation of (154) would lead to the quinone enol (77) which could have been compared with the product from the

oxidation of (74). Clearly oxidation of (154) even at the lower potential of + 0.8 volts results in the formation of tars and in fragmentation reactions, and no isolable products are formed. The difference in the electrochemical behaviour of the 2-acylindole (154) and the 3-acylindole (74) may be due to the fact that (74) is a vinylogous amide. (The indole (74) was in fact originally synthesised as part of a study of the anodic oxidation of amides[8].) Also, in (154) the 3-position is unsubstituted and so polymerisation may occur (scheme 6). Much time had been devoted to the synthesis of (154) and it was disappointing that anodic oxidation of the compound failed to give any useful information or identifiable products.

Itahara[44] has cyclised 1-methyl-3-benzoylindole (127) to (128) by the action of palladium (II) acetate. This is interesting since, as has already been noted, electrochemical coupling does not occur with the higher homologue (73) and it seems that the side chain has to consist of at least three atoms as in (74) before intramolecular cyclisation is observed. Ring size does not present a problem in palladium promoted coupling reactions because the palladium atom is present in the intermediate thus increasing the effective ring size (scheme 22). The aryl ring is palladated ortho to the carbonyl function with the loss of one molecule of acetic acid. The organometallic intermediate then cyclises with loss of "HPdOAc" in a concerted process. The first step of the cyclisation is the formation of a π-complex which holds the molecule in the correct orientation for coupling to occur.

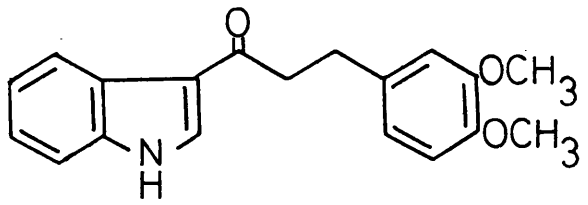
It was thought that treatment of 3-(3,4-dimethoxyphenylpropanoyl)-indole (74) with palladium acetate would induce cyclisation to form (185). The structure of this compound should be unambiguous because

Scheme 22

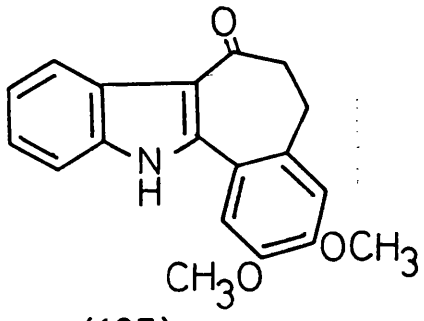


there would not be a spiro-intermediate in the reaction sequence. Anodic oxidation of (185) could be carried out, hopefully leading to the quinone (76) which could be compared with the anodic oxidation product from (74) in order to establish the true structure of this compound.

All the substrates which Itahara[44] used in his work were 1-substituted indoles; however, this is probably not necessary since there are examples in the literature of palladium acetate reactions with NH compounds[45]. Itahara also used only 0.5 equivalents of



(74)



(185)

palladium acetate per equivalent of substrate. There is no apparent reason for this since the palladium acetate plays a stoichiometric part in the reaction.

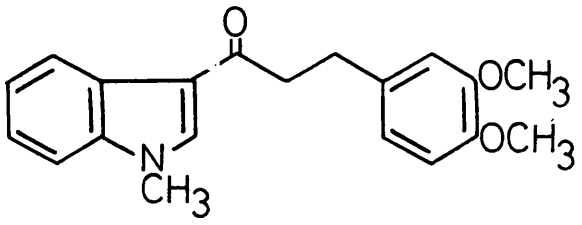
The indole (74) was treated with palladium acetate (0.5 mol/mol of indole) in boiling acetic acid. Work-up gave a mixture which could not be separated by column chromatography, all the components having similar R_f values with all the thin layer chromatography systems used. The mixture consisted mainly of starting material but mass spectrometry also showed molecular ions at $\underline{m/e}$ 351 and 307, the former corresponding to acetylated starting material and the latter probably corresponding to the required product (185). The reaction was repeated using 1:1 molar equivalents of (74) and palladium acetate. The mass spectral peak at $\underline{m/e}$ 307 was more intense than in the previous experiment but only the returned starting material could be isolated; further separation proved impossible even by preparative liquid chromatography.

It is possible that some of the palladium acetate was used up in acetylating the substrate since indoles are not acetylated by acetic acid. Thus the reaction was repeated using two molecular equivalents of palladium acetate, but again pure products could not be separated.

It is reported[46] that aryl-aryl coupling reactions can be made catalytic with respect to palladium (II) by the addition of copper (II) acetate. The copper (II) ion is able to reoxidise the deposited palladium (O) to palladium (II). The oxidation is also catalytic with respect to copper (II) because acetic acid will oxidise copper (I) to copper (II). With this in mind the reaction was repeated under these conditions but it proved unsuccessful and the mass spectrum of the product only showed peaks at $\underline{m/e}$ 351 and 309, no peak was observed at $\underline{m/e}$ 307. The use of acetonitrile as solvent in palladium acetate reactions is reported[46] to give higher yields of products than when acetic acid is employed and the catalytic reaction is also best carried out under oxygen rather than air. In the event, however, the use of acetonitrile and oxygen was to no avail, only starting material was returned with no evidence for any acetylation reactions. In a final attempt at carrying out a palladium acetate promoted intramolecular coupling of (74) to (185) the stoichiometric reaction was repeated with acetonitrile as solvent, but again only starting material was obtained.

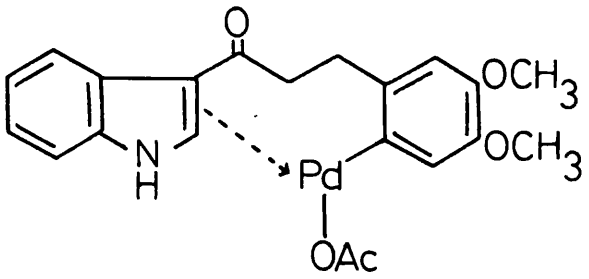
It was decided that the N-methyl derivative (186) of (74) should be prepared and oxidised with palladium acetate. The indole (74) was treated with potassium hydroxide in dimethylsulphoxide to form the amion, and then treated with iodomethane to give the methylated derivative (186). Treatment of (186) with palladium acetate in acetic

acid again failed to induce intramolecular coupling. Mass spectrometry and thin layer chromatography (silica/ether) showed the resultant solid to consist almost entirely of starting material.

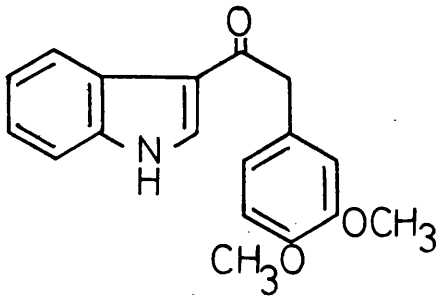


(186)

The length of the side chain linking the two aromatic systems in (74) may have adversely affected the reaction. The initial step in the reaction is palladation of the dimethoxyphenyl ring. The next step is intramolecular attack to form an intermediate π-complex (187). This step may be inhibited by the long side chain on conformational grounds.

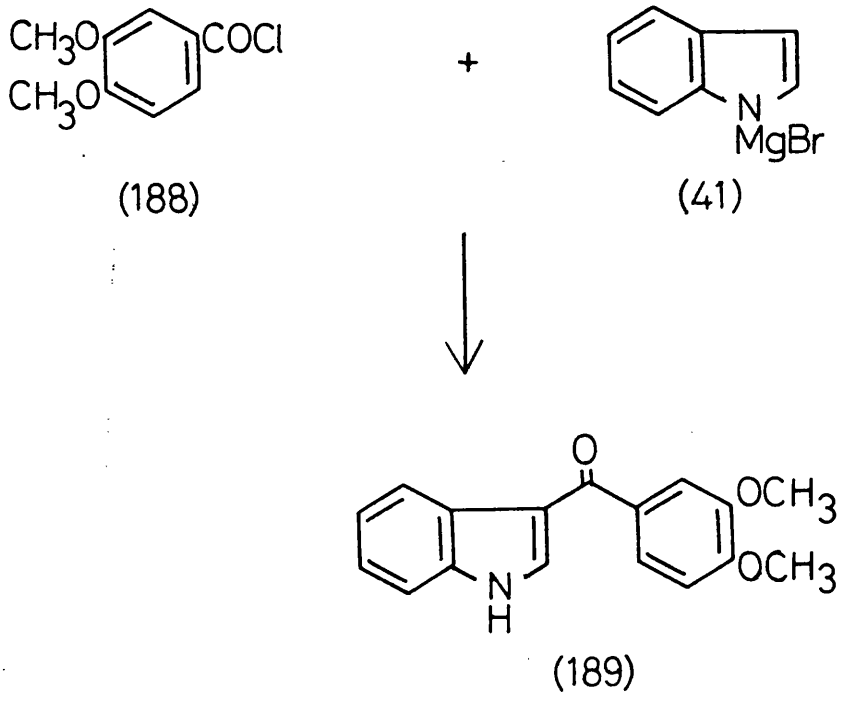


(187)



(73)

To test this speculation the lower homologue (73) was prepared by treatment of indole magnesium bromide (41) with 3,4-dimethoxyphenylacetyl chloride (142) but surprisingly treatment of (73) with palladium acetate failed to cause cyclisation. It had been thought that the shorter side chain might aid the formation of a π-complex and so assist the intramolecular coupling reaction. The next lower homologue 3-(3,4-dimethoxybenzoyl)indole (189) was then prepared by the reaction of indole magnesium bromide (41) with 3,4-dimethoxybenzoyl chloride (188).



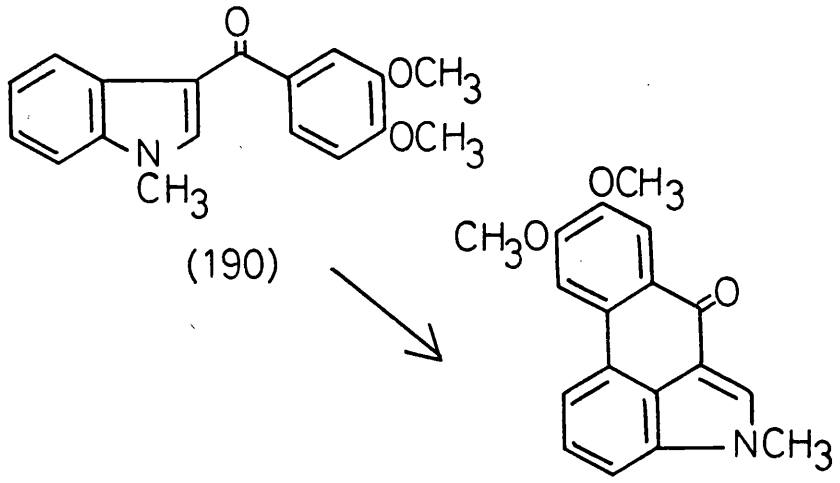
(188) (41)

(189)

When (189) was treated with palladium acetate in acetic acid all of the starting material was consumed and the residue after evaporation of the solvent was subjected to column chormatography on silica gel with ether as eluent. Most of the material was a tarry substance which remained on the column, but a trace quantity of a yellow solid was obtained with a molecular ion peak in the mass spectrum at $\underline{m/e}$ 279, which was most probably a cyclised product. However, the yield was far too low for positive identification. The reaction was repeated under milder conditions using acetonitrile as solvent, but in this case no reaction occurred at all.

3-(3,4-Dimethoxybenzoyl)indole (189) was N-methylated with iodomethane and potassium hydroxide in dimethylsulphoxide. The 1-methyl derivative (190) is identical to the substrate (127) used by Itahara[44] except for the presence of the two methoxy functions. Palladium acetate oxidation of this compound should show whether the failure of the previous reactions was due to the presence of the methoxy groups in the aromatic ring or to some other factor. 1-Methyl-3-(3,4-dimethoxybenzoyl)indole (190) was thus treated with palladium acetate in glacial acetic acid and the tetracyclic compound (191) was formed and purified by column chromatography. The isolated yield of this compound was small because the compound streaked on the column and had a similar R_f value to the residual starting material which was present. However, sufficient material was obtained from the end of the column for complete characterisation.

This product was unexpected because Itahara[44] had only observed cyclisation at the 4-position of the indole ring when the 2-position was blocked. In other cases the coupling occurred exclusively at the 2-position. Evidence for this structure was found in the absence of

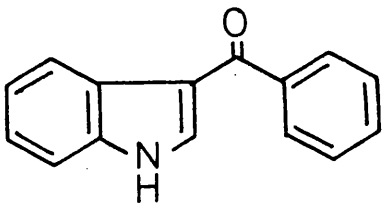


any signal above 8 ppm in the ^{1}H n.m.r. spectrum. Such a signal would be expected for the proton in the 4-position of a 3-acylindole. Also, the presence of two singlet aromatic peaks indicates the substitution position in the dimethoxyphenyl ring.

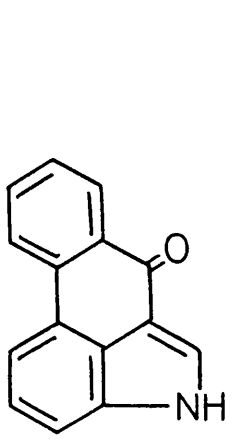
It was decided to prepare 3-benzoylindole (192) and then to treat it with palladium acetate and compare the result with that obtained by Itahara for the 1-methyl derivative (127). Treatment of benzoyl chloride with indole magnesium bromide (41) gave (192) in the usual way. Treatment of (192) with palladium acetate followed by column chromatography gave two products. The tetracyclic compound (193) analogous to (191) was formed in 34% yield. This again is unusual; there was no evidence for the formation of any product cyclised at the 2-position analogous to (128). It is difficult to understand why Itahara observed coupling only at the 2-position with (127) whereas palladium acetate treatment of (192) under identical

conditions leads to cyclisation at the 4-position.

The other product isolated from the column was a crystalline solid with a molecular ion at $^{m}/_{e}$ 325 in the mass spectrum and a major fragmentation peak at $^{m}/_{e}$ 105. The infra-red spectrum showed no N-H absorption, but two absorptions due to carbonyl groups were observed. The product was found to be 1,3-dibenzoylindole (194). The mode of formation of this product is very difficult to understand, the palladium acetate has somehow caused the transfer of a benzoyl group from the 3-position of one molecule to the 1-position of another. The reaction is without precedent in the literature and no explanation can be offered for its occurrence at the present time.



(192)



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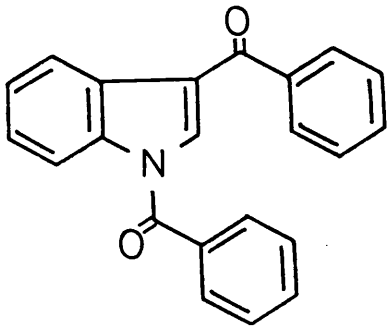
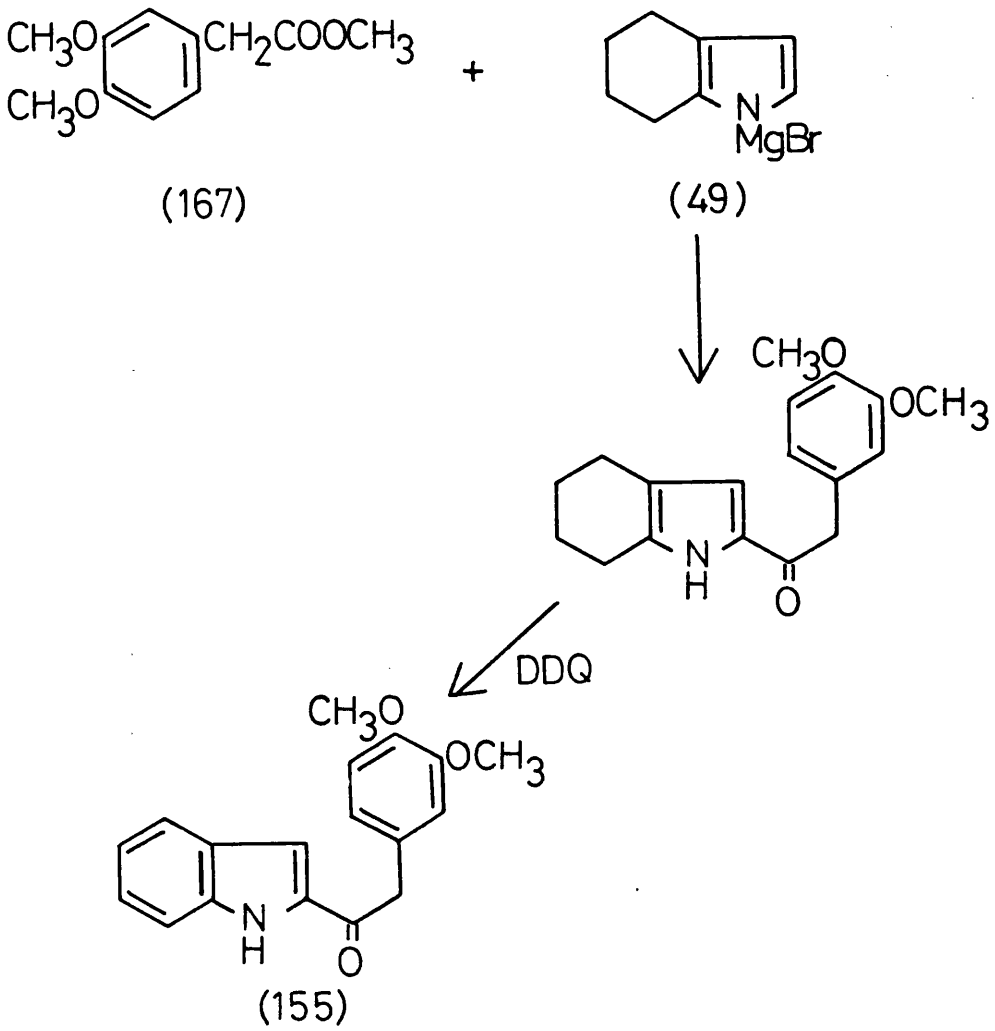


(194)

The results obtained here for palladium acetate coupling reactions indicate that cyclisation can occur for 3-benzoylindoles but not for other 3-acylindoles. Possibly the carbonyl group has to be conjugated to another aromatic system as well as to the indole ring thereby decreasing the vinylogous amide character of the 3-acylindole, or it may be that benzylic oxidation is a competing reaction in substrates bearing phenyl methyl units. One may also conclude that it is not necessary to use 1-alkylindoles as substrates, the cyclisations will occur even for indoles unsubstituted at the 1-position but N-acylation may then be a problem. It would also appear that in these particular reactions acetic acid is a better solvent than acetonitrile.

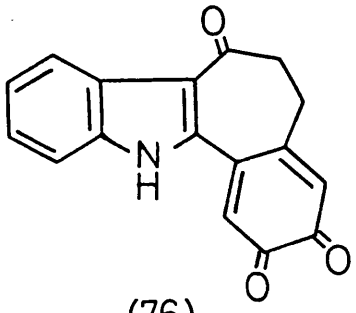
One final palladium acetate oxidation was carried out using 2-(3,4-dimethoxyphenylacetyl)indole (155). This compound, being a 2-acylindole is not a vinylogous amide and so the comments made above may not apply. The compound (155) had been prepared for electrochemical studies but had not been used because the result for the homologue (154) suggested that only polymerisation would occur due to the unsubstituted 3-position. The compound (155) was prepared by treating methyl 3,4-dimethoxyphenylacetate (167) with 4,5,6,7-tetrahydroindole magnesium bromide (49) followed by aromatisation with dichlorodicyanobenzoquinone. The second step only proceeded in low yield and most of the material was transformed to a tar. Treatment of (155) with palladium acetate only gave an intractable tar, presumably due to acid-catalysed polymerisation at the unsubstituted 3-position.



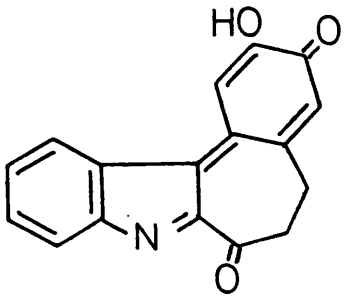
Thallium (III) trifluoroacetate is another chemical agent which has been used to effect coupling reactions. 3-(3,4-Dimethoxyphenyl-propanoyl)indole (74) was treated with thallium trifluoroacetate in dichloromethane[47]. The substrate failed to react and the oxidant decomposed within a few minutes causing the solution to develop a dark red colour. The reagent is assumed to mimic anodic reactions in so far as it oxidises aromatic rings to radical cations. In this experiment the highly reactive reagent decomposed before it had effected oxidation of the substrate. It is reported[48] that thallium trifluoroacetate is

light sensitive and so future reactions with this reagent were carried out in the dark. The reaction was repeated in dichloromethane at -78° and in the dark[49]. Again the substrate failed to react. A final attempt at this reaction was made using trifluoroacetic acid[50] as solvent. Work-up gave an intractable red tar. Thin layer chromatography showed the presence of many components which could not be separated.

The final part of the work on indoles was a last attempt to determine the structure of the product from the anodic oxidation of (74).



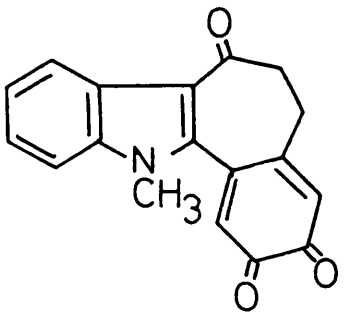
(76)



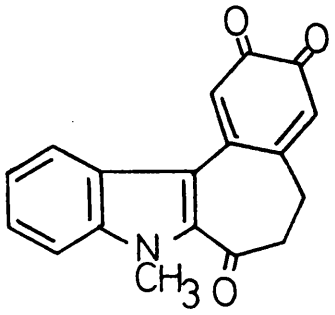
(77)

Since it is not possible to distinguish between the two proposed structures (76) and (77) by conventional spectroscopic methods it was proposed that the 1-methyl derivative (186) of (74) be subjected to anodic oxidation. The two possible products would now be (195) and (196); enolisation of (196) is prevented by the presence of the methyl group in the 1-position. It should be possible to distinguish between these two structures by nuclear Overhauser experiments. Irradiation at the frequency corresponding to the methyl group would cause

enhancement of the signal corresponding to the proton in the 7-position of the indole ring in both cases, but only in (195) would one of the signals due to the protons in the quinone ring also be enhanced. These signals would be seen as one proton singlets and would thus be easily identified. Nuclear Overhauser experiments in the N-demethyl series were not attempted because of the lack of the appropriate "close" geometries.



(195)



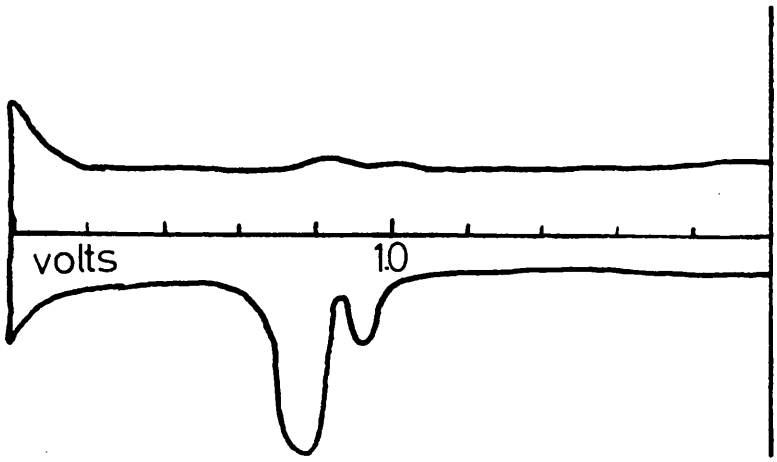
(196)

The cyclic voltammogram of (186) shows oxidation peaks at potentials of + 1.08 and + 1.22 volts (figure 13). The indole (186) was electrolysed at an anode potential of + 0.9 - 1.2 volts. Thin layer chromatography (silica/ether) showed two components, starting material (186) and a red compound of the same R_f value. Column chromatography returned the starting material (60%) but the other component decomposed on the column and all the red colouration faded. There was not sufficient time left to repeat this experiment, but at a future date careful isolation of the dark red product from the oxidation may well provide the solution to the as-yet unanswered question of the structure of the product from the anodic oxidation of

3-(3,4-dimethoxyphenylpropanoyl)indole (74).

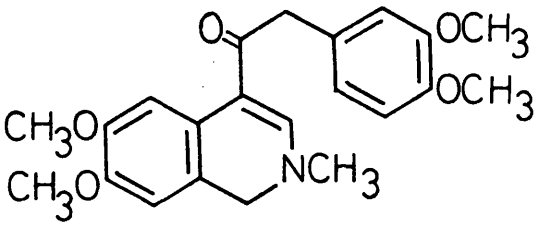
Figure 13

Cyclic Voltammogram of 1-Methyl-3-(3,4-dimethoxyphenylpropanoyl)indole (186)

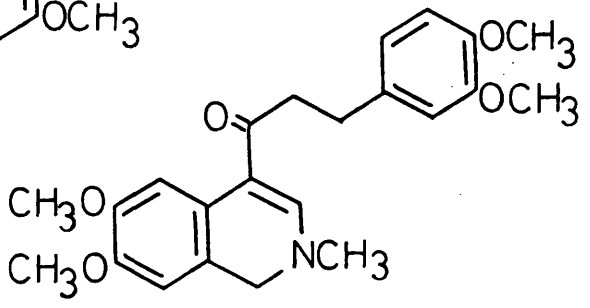


Chemical and Electrochemical Oxidations of Isoquinolines

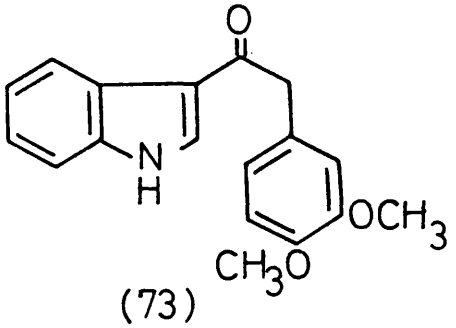
Concurrent with the work on indoles a series of experiments was also under way with isoquinolines. The first isoquinoline substrates chosen for electrochemical studies were two homologous 4-acyl-1,2-dihydroisoquinolines (197) and (198). It will be seen that these compounds are analogous to the 3-acylindoles (73) and (74) respectively. 1,2-Dihydroisoquinolines are enamines and are generally highly reactive, but in (197) and (198) the enamine structure is stabilised by conjugation with a carbonyl group forming a vinylogous amide structure.



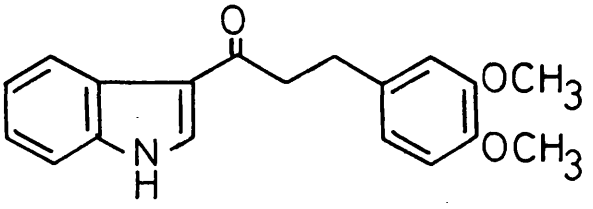
(197)



(198)



(73)

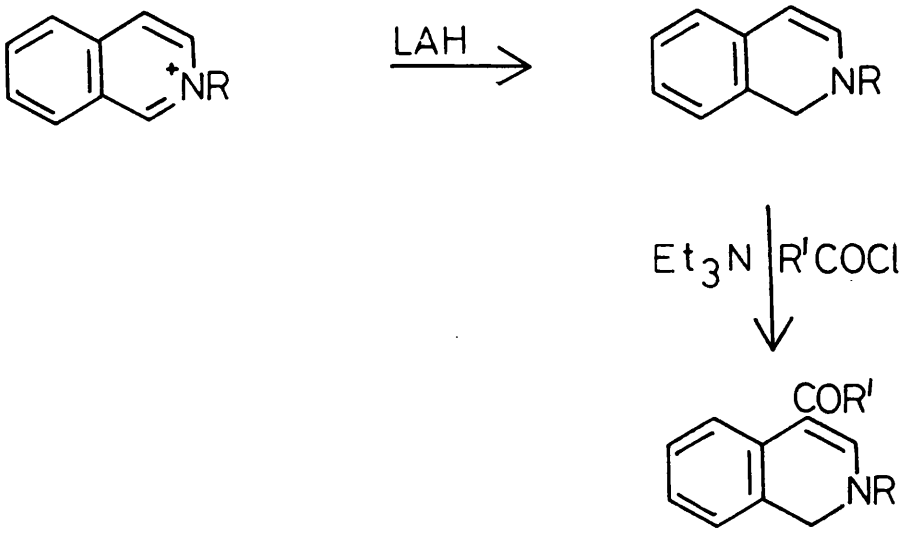


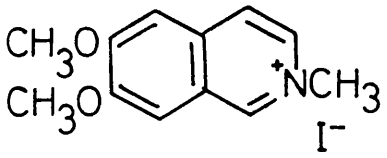
(74)

It is possible that these compounds will behave like the indoles already studied on electrolysis. The initial electron loss will most probably be from the dimethoxyphenyl ring; attack will then occur at the electron-rich 4-position to give a spiro-intermediate which will undergo a rearrangement. If this is so then (197) will not cyclise because of the disfavoured five membered ring in the intermediate, and like the indole (73) be electrochemically inert. On the other hand the higher homologue (198) may cyclise just as the indole (74) underwent a coupling reaction.

4-Acyl-1,2-dihydroisoquinolines were first prepared by treating 1,2-dihydroisoquinolines with acid chlorides in the presence of triethylamine[51] and the starting 1,2-dihydroisoquinolines themselves were simply made by reducing the appropriate isoquinolinium salts with lithium aluminium hydride (scheme 23).

Scheme 23

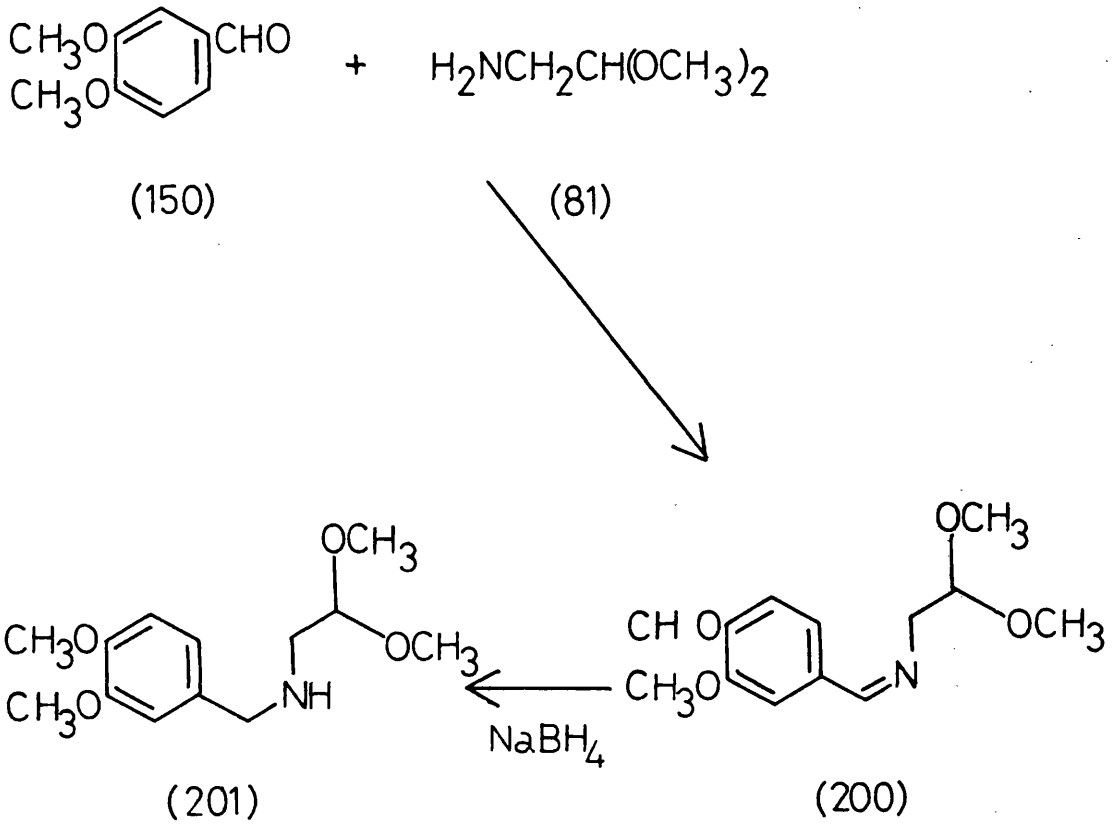




(199)

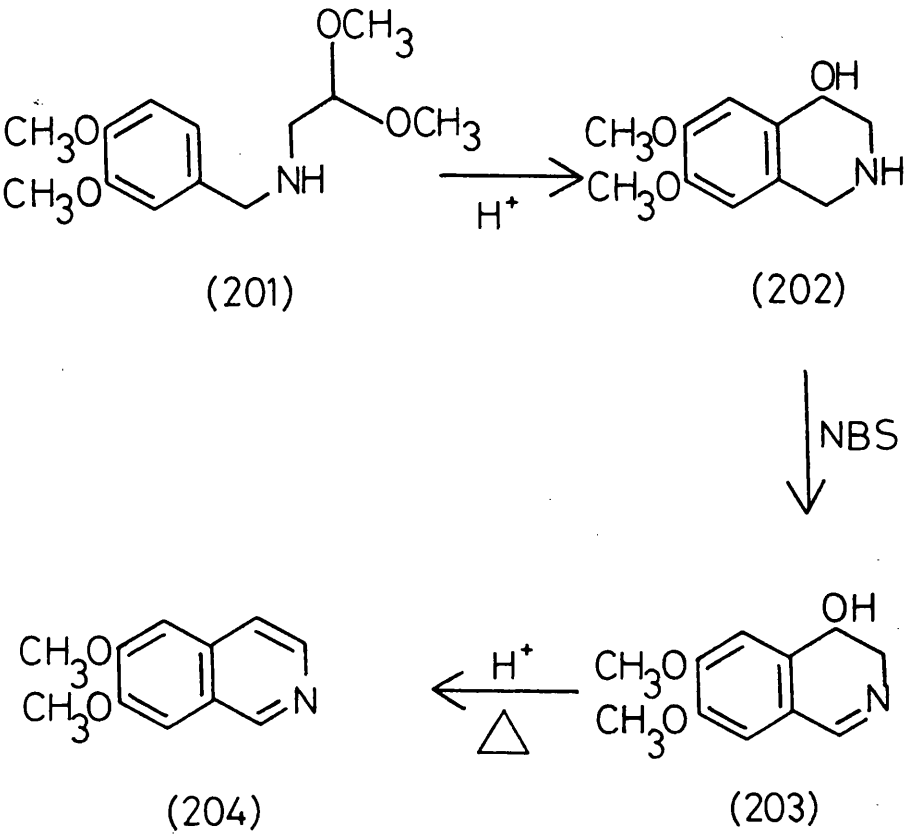
This acylation procedure generally gives poor yields and a better method involves the use of N,N'-dicyclohexylcarbodiimide ($C_6H_{11}N=C=NC_6H_{11}$). This reagent is an acylating agent often used in the synthesis of peptides but here the 1,2-dihydroisoquinoline is treated with a carboxylic acid in the presence of N,N'-dicyclohexylcarbodiimide and a 4-acyl-1,2-dihydroisoquinoline results along with N,N'-dicyclohexylurea ($C_6H_{11}NHCONHC_6H_{11}$).

The first stage in the synthesis of the isoquinoline derivatives (197) and (198) is the preparation of 2-methyl-6,7-dimethoxyisoquinolinium iodide (199). This compound was prepared by modifications of the Pomeranz-Fritsch reaction; thus 3,4-dimethoxybenzaldehyde (150) was condensed with aminoacetaldehyde dimethylacetal (81) to form the Schiff base (200) by stirring at room temperature in ethanol for one hour. This compound was reduced <u>in situ</u> with sodium borohydride to give 3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (201). Compound (201) was the starting point for three different modified Pomeranz-Fritsch reactions leading to 6,7-dimethoxyisoquinoline (204) which was isolated as its methiodide salt (199).



The first stage in the isoquinoline synthesis designed by Bobbitt[52] involves the acid catalysed cyclisation of (201) to 4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (202)[53]. The acetal (201) is treated with 6N hydrochloric acid at room temperature. The acetal is hydrolysed to the aldehyde and this then cyclises to give (202). Treatment of (202) with N-bromosuccinimide in chloroform at room temperature gives 4-hydroxy-6,7-dimethoxy-3,4-dihydroisoquinoline (203) as its hydrobromide salt, and dehydration of (203) by heating in 6N ethanolic hydrochloric acid gives the

required 6,7-dimethoxyisoquinoline (204).



(201) (202) (204) (203)

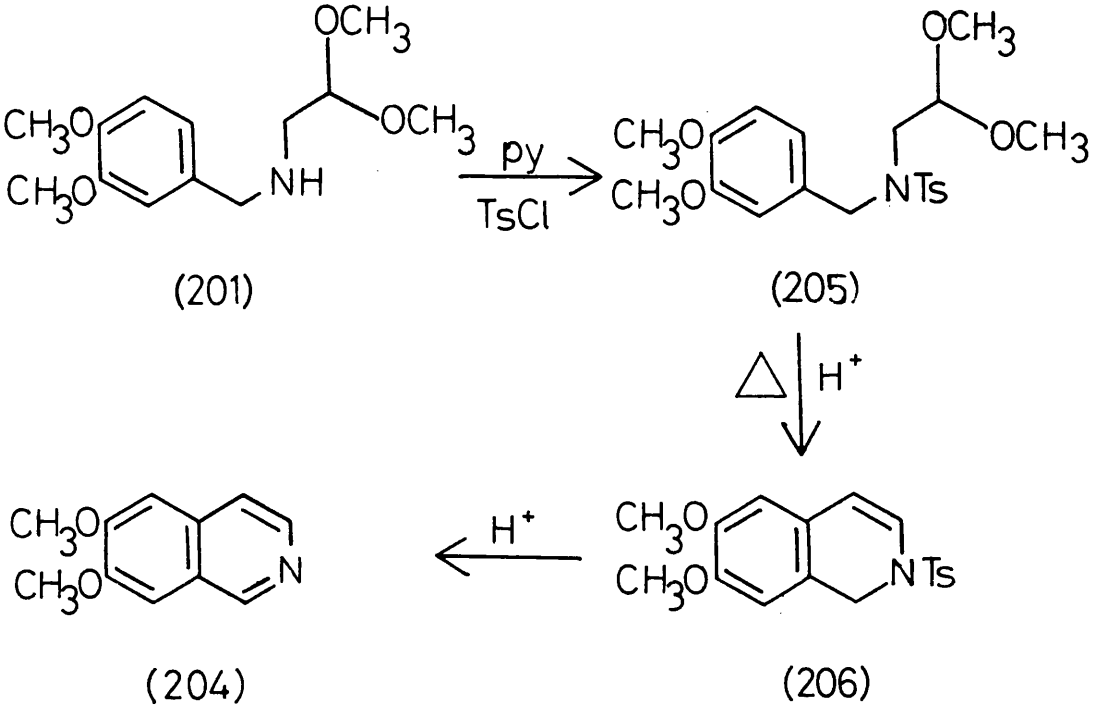
Problems were experienced with this route and the hydroxy compound (202) could only be isolated in low yield. In our first attempt the acetal (201) was dissolved in 6N ethanolic hydrochloric acid and stirred at room temperature for twenty hours. Work-up of the reaction gave an intractable gum. During this last procedure the reaction product was warmed whilst the solvent was evaporated under reduced pressure. It seems likely that heating (202) in a solvent causes dehydration to occur resulting in the formation of a reactive 1,2-dihydroisoquinoline which disproportionates and

polymerises giving a complex mixture[52] and in view of this the reaction was next repeated under more controlled temperature conditions but the isolated yield of (202) was only 4%. The yield reported in the literature[54] is 69%.

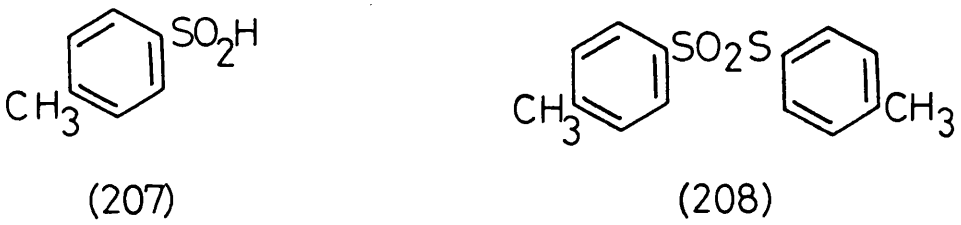
An alternative route to the isoquinoline (204) has been proposed by Jackson[55]. This method is reported to give a higher yield than the corresponding Bobbitt synthesis and was used successfully in this thesis. The acetal (201) was treated with toluene-4-sulphonyl chloride (TsCl) in pyridine to give the tertiary amine (205). The tosylamine (205) was converted to the isoquinoline (204) in one step by treatment with hydrochloric acid in boiling dioxan. It is considered that the tosylamine (205) cyclises in the usual way by acid catalysed hydrolysis of the acetal, cyclisation and dehydration giving the 2-tosyl-1,2-dihydroisoquinoline (206) which then eliminates toluene-4-sulphinic acid (207) giving the isoquinoline (204). It is interesting to note that work-up of the non-basic material from this reaction afforded not toluene-4-sulphinic acid (207) but the S-(4-methylphenyl) ester of toluene-4-sulphothioic acid (208). This compound is reported[56] to result from disproportionation of the aromatic sulphinic acid under acid conditions.

The isoquinoline (204) was dissolved in acetone and treated with iodomethane. A precipitate of the methiodide salt (199) formed instantaneously, and this was collected and recrystallised. The overall yield of methiodide (199) from acetal (201) was 61%.

The third isoquinoline synthesis used in this thesis was that reported by Watanabe[57]. Treatment of the acetal (201) with cold chlorosulphonic acid led directly to the isoquinoline (204). The yield in this preparation was only 48% and so the tosylamine route



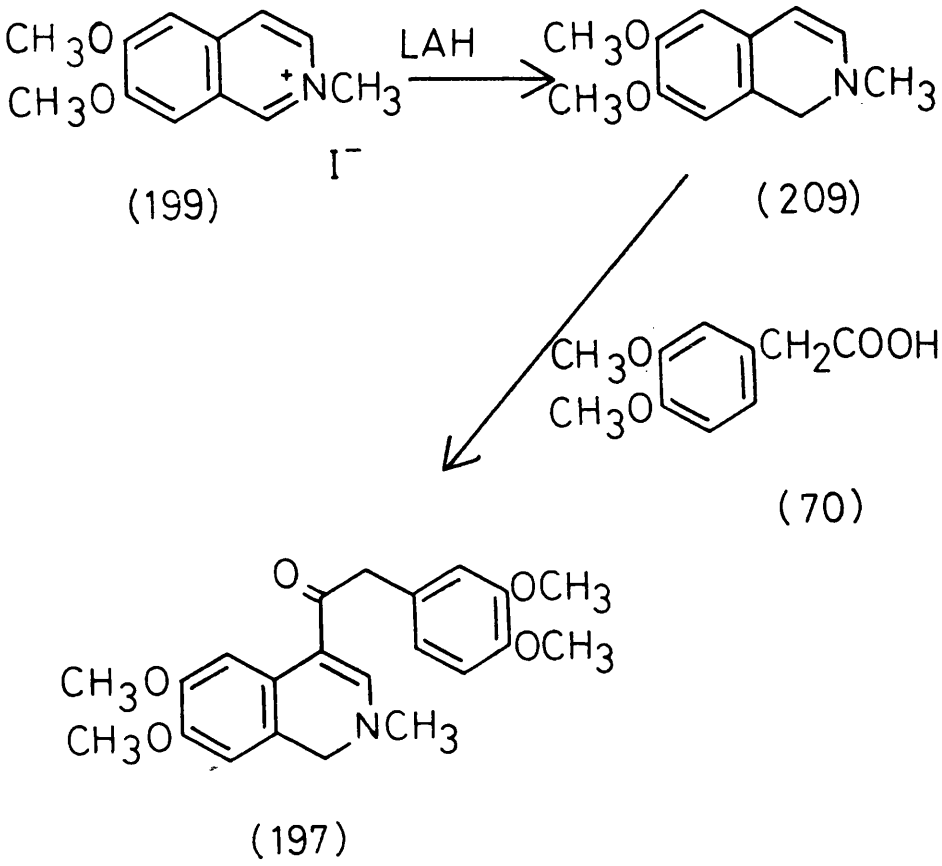
(201) (205) (204) (206)



(207) (208)

proved to be the method of choice.

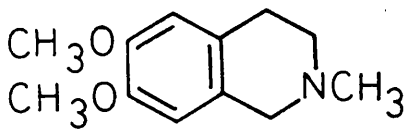
2-Methyl-6,7-dimethoxyisoquinolinium iodide (199) was thoroughly dried in vacuo and reduced with lithium aluminium hydride. The resultant solution of the 1,2-dihydroisoquinoline (209) was treated with N,N'-dicyclohexylcarbodiimide and then with 3,4-dimethoxyphenylacetic acid (70). Work-up of the reaction afforded 2-methyl-4-(3,4-dimethoxyphenylacetyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (197).



The cyclic voltammogram (figure 14) of (197) shows three oxidative peaks at anodic potentials of + 0.55, 0.8 and 1.2 volts. This compound is thus more active electrochemically than the indole (73) which only showed a redox couple at + 1.2 volts in the cyclic voltammogram. The substrate (197) was electrolysed at an anode potential of + 1.2 volts until the current had dropped to below 10mA. The result was a black tar from which no products were isolated. The mass spectrum of the tar showed a major peak at $\frac{m}{e}$ 207 and we speculate that this is due to 2-methyl-6,7-dimethoxy-1,2,3,4-tetra-

hydroisoquinoline (210). The question of how this product is formed remains unsolved for both fragmentation of the substituent in the 4-position and reduction, or disproportionation, of the product radical is required.

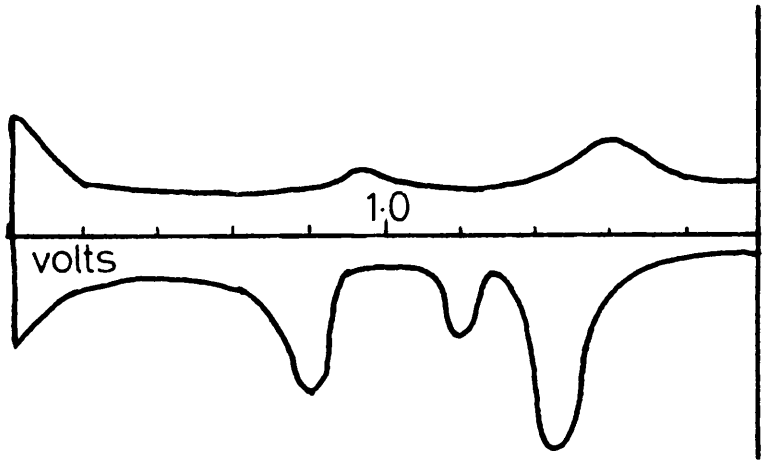
The electrolysis was repeated at the lower potential of + 0.8 volts, but again only a tarry mixture of products resulted. This contrasts sharply with the behaviour of the indole (73) which is returned unchanged on electrolysis. The peak at + 1.2 volts in the cyclic voltammogram (figure 14) is due to ionisation of the dimethoxyphenyl ring but it is difficult to explain the origin of the other two peaks. Presumably one peak must be due to oxidation of the nitrogen lone pair of electrons, but this was unexpected since the nitrogen is part of the vinylogous amide chromophore; moreover, the compound is known to be non-basic because it moves up a silica thin layer chromatography plate in low polarity solvents such as ether and dichloromethane. In view of this, facile oxidation of the nitrogen lone pair would not have been predicted.



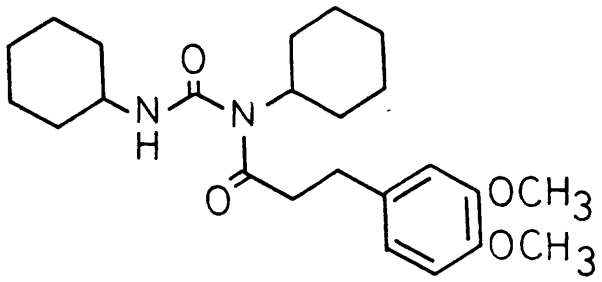
(210)

Figure 14

Cyclic Voltammogram of 2-Methyl-4-(3,4-dimethoxyphenylacetyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (197)



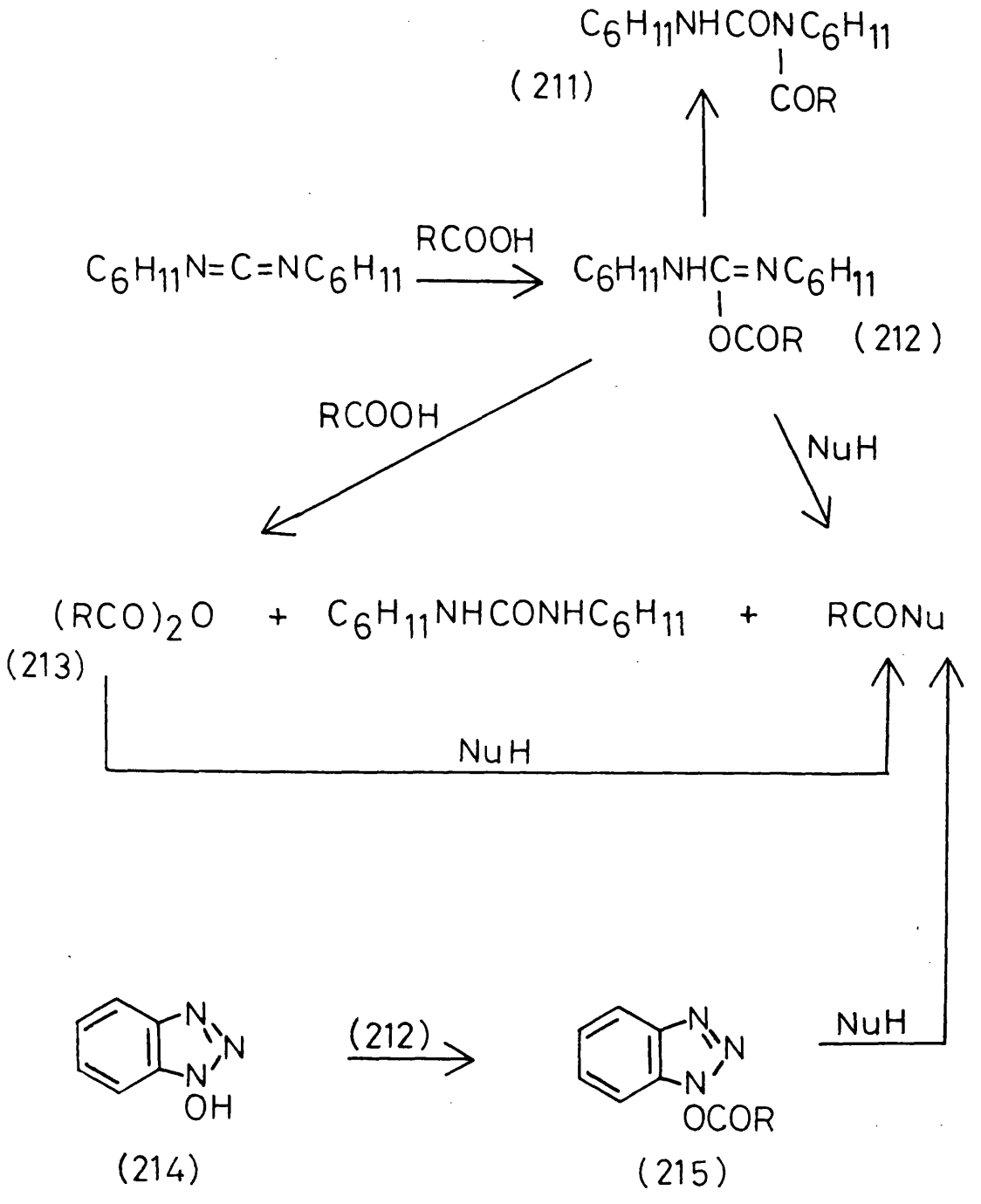
Several attempts were made to synthesise 2-methyl-4-(3,4-dimethoxyphenylpropanoyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (198) but none was successful. The 1,2-dihydroisoquinoline (209) was prepared as before and then treated with N,N'-dicyclohexylcarbodiimide, and 3,4-dimethoxyphenylpropanoic acid (153). Work-up of the reaction gave a crystalline solid which was shown to be the N-acylurea (211).



(211)

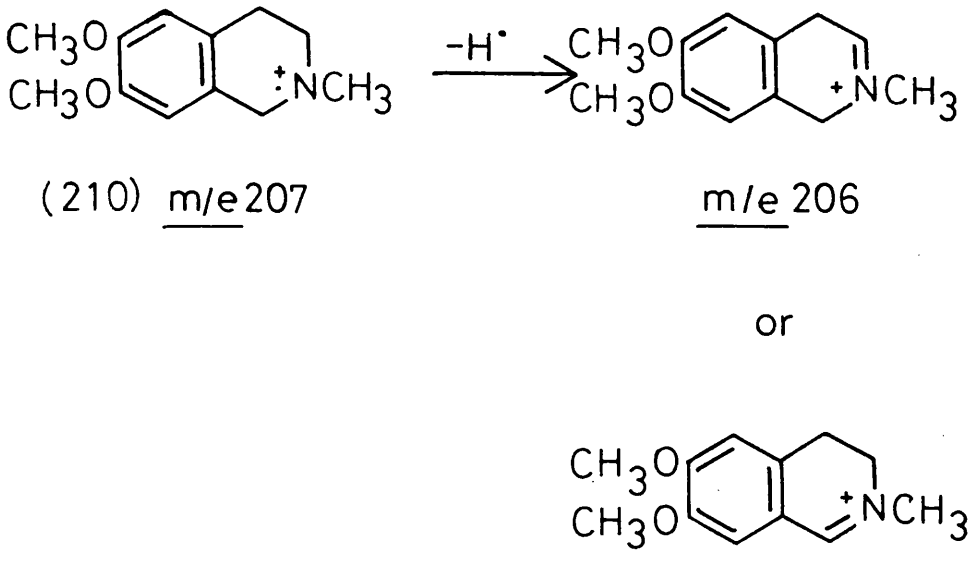
N,N'-Dicyclohexylcarbodiimide reacts[58] with acids forming O-acylisoureas (212). These can be captured by alcohols or amine nucleophiles, or they can react with more acid to give symmetrical anhydrides (213). The latter can then react with the nucleophiles. One major disadvantage in the use of the reagent is competitive intramolecular rearrangement of the reactive O-acylisourea (212) to the inert N-acylurea (211, scheme 24)[59]. The rearrangement reaction can largely be avoided by interception of the O-acylisourea (212) with 1-hydroxybenzotriazole (214)[60]. The ester (215) so formed is a powerful acylating agent which reacts with the nucleophile.

Scheme 24


C6H11NHCONC6H11
COR
(211)
C6H11N=C=NC6H11
RCOOH
C6H11NHC=NC6H11
OCOR
(212)
RCOOH
NuH
(RCO)2O
(213)
+
C6H11NHCONHC6H11
+
RCONu
NuH
N
N
N
OH
(214)
(212)
N
N
N
OCOR
(215)
NuH

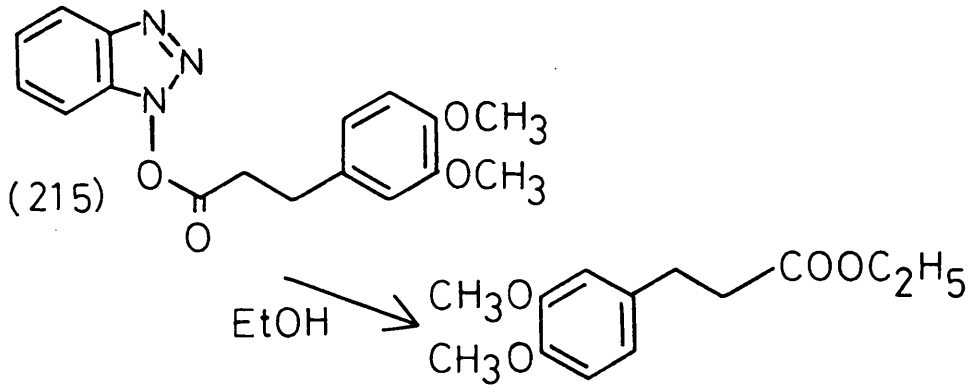
The 1,2-dihydroisoquinoline (209) was prepared again and then treated with 3,4-dimethoxyphenylpropanoic acid (153), 1-hydrobenzotriazole (214) and N,N'-dicyclohexylcarbodiimide. On work-up a gum was obtained and this was triturated with ethanol. Crystallisation could not be induced by trituration and so the gum was separated into basic and non-basic components. The basic fraction was shown to contain the tetrahydroisoquinoline (210) and also intractable polymeric material. The mass spectrum at an ionising energy of 10 electron volts showed a peak at $^{m}/e$ 207, but at 70 electron volts

Scheme 25



the major peak was at $\frac{m}{e}$ 206. The loss of a hydrogen atom from the 1- or the 3-position in the high energy spectrum is characteristic of a tetrahydroisoquinoline (scheme 25).

The non-basic fraction was found to consist mainly of ethyl 3,4-dimethoxyphenylpropanoate (216) and so the triazole ester (215) had failed to acylate the 1,2-dihydroisoquinoline (209) and had remained intact until the product was triturated with ethanol. The ethanol acted as a nucleophile resulting in the formation of the ethyl ester (216) and 1-hydroxybenzotriazole (214). The triazole (214) was not found in either of the above two fractions since it is water soluble and was removed when the organic solutions were washed.

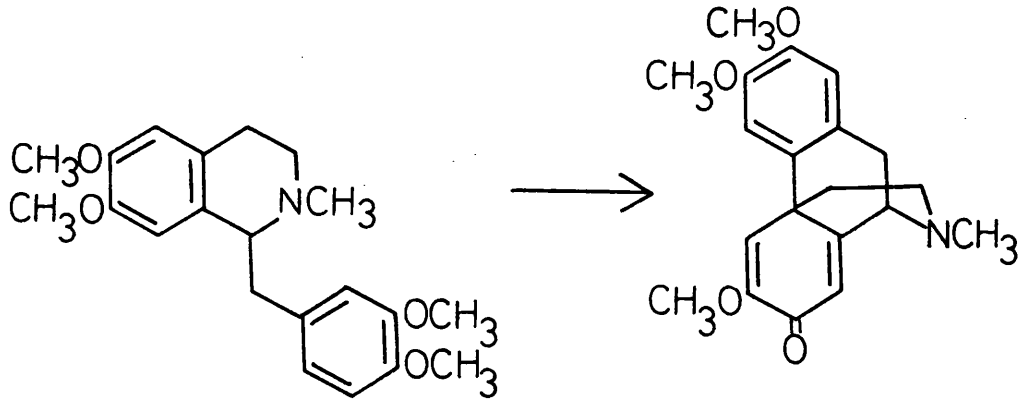


In a final attempt to synthesise (198), the classical route[51] to 4-acyl-1,2-dihydroisoquinolines was employed. The 1,2-dihydroisoquinoline (209) was prepared as above and then treated with 3,4-dimethoxyphenylpropanoyl chloride (149) in the presence of a molar equivalent of triethylamine. After work-up a gum was obtained; thin layer chromatography showed the presence of many components. None of the products could be identified, but mass spectrometry again

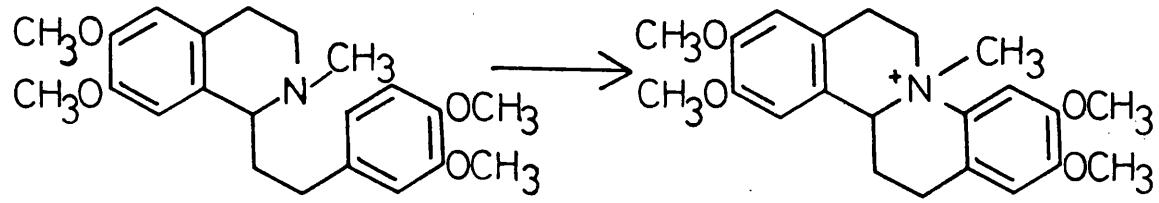
indicated the presence of the tetrahydroisoquinoline (210).

All three of these synthetic routes which are recommended in the literature have here failed to effect acylation of 2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline (209). No explanation can be offered for the apparent difference in behaviour between the phenylacetyl and the phenylpropanoyl derivatives.

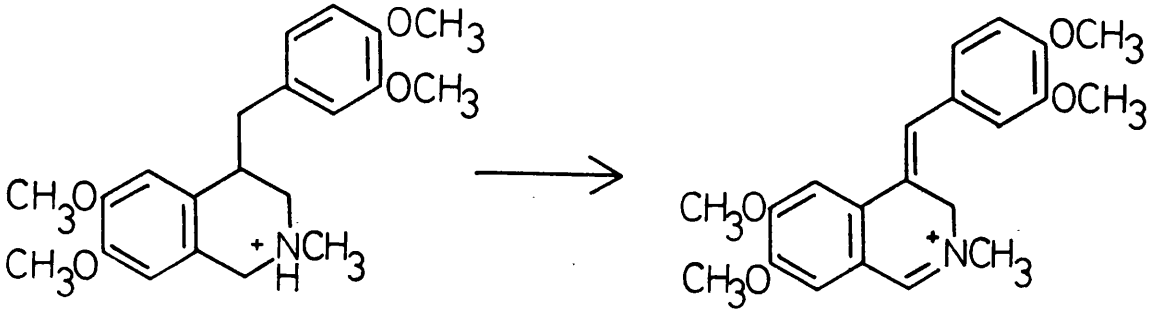
The last series of oxidations to be carried out in this thesis involved the two homologous 4-substituted tetrahydroisoquinolines (220) and (233). Miller[61] has oxidised the 1-benzyl compound landanosine (101) to O-methylflavinantine (102), and Sainsbury and Najafi[62] have oxidised the 1-phenethyl derivative (105) to the tetracyclic salt (106). The hydrochloride salt of the 4-benzyl isomer (103) of landanosine has been oxidised[63] to the 4-benzylidene-3,4-dihydroisoquinoline salt (104).



(101) (102)



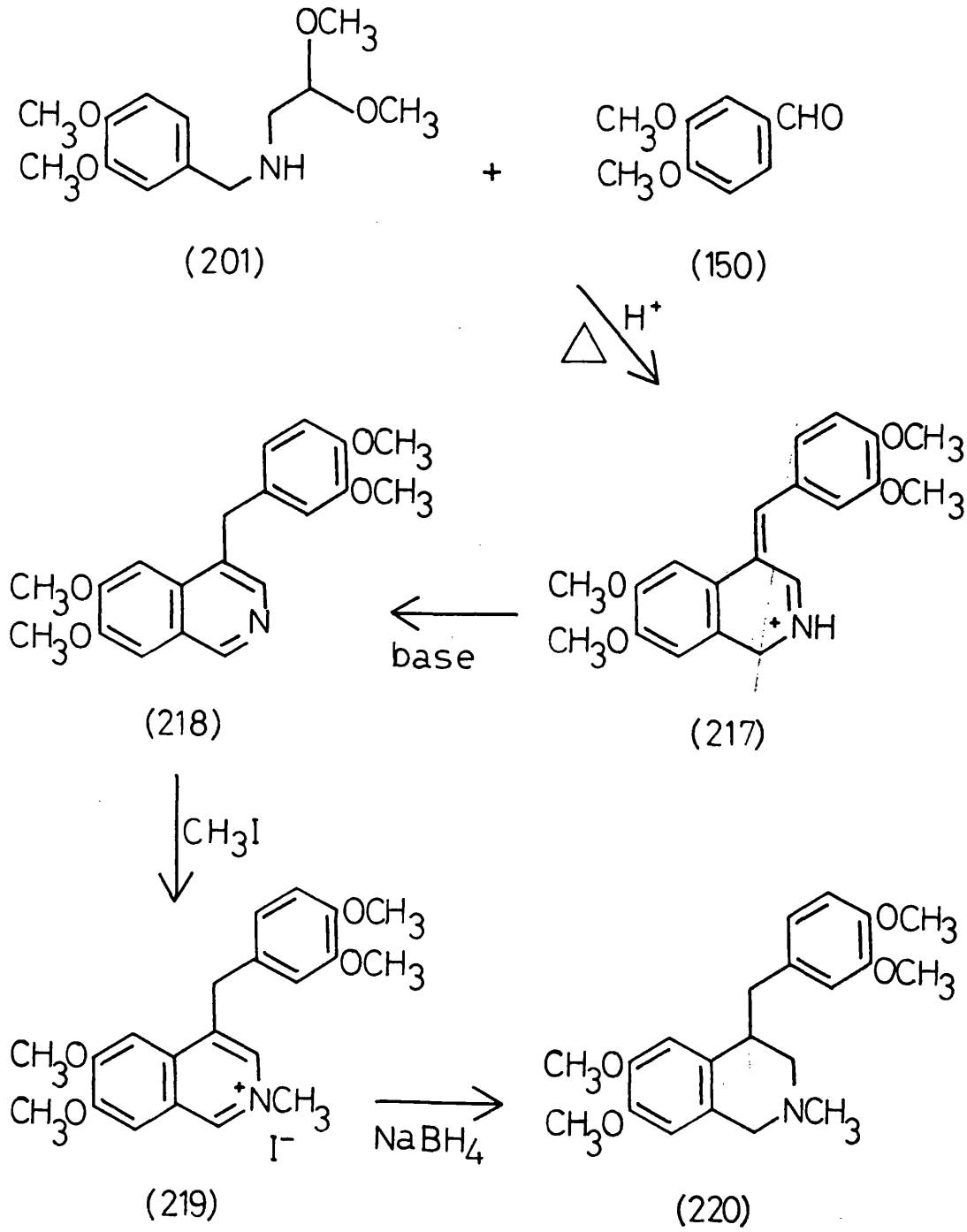
(105) (106)



(103) (104)

To complete this group of anodic reactions 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (233) was prepared and subjected to electrochemical oxidation. Compound (103) had been oxidised in the form of the hydrochloride salt in order to prevent the oxidation of the nitrogen lone pair of electrons, and no coupling was observed in the product. In view of Miller's[64] comments concerning the favourable anchimeric assistance of the lone pair electrons in the low potential oxidation of landanosine it was decided to repeat the oxidation of (103) but this time to use the free base (220) instead of the hydrochloride salt.

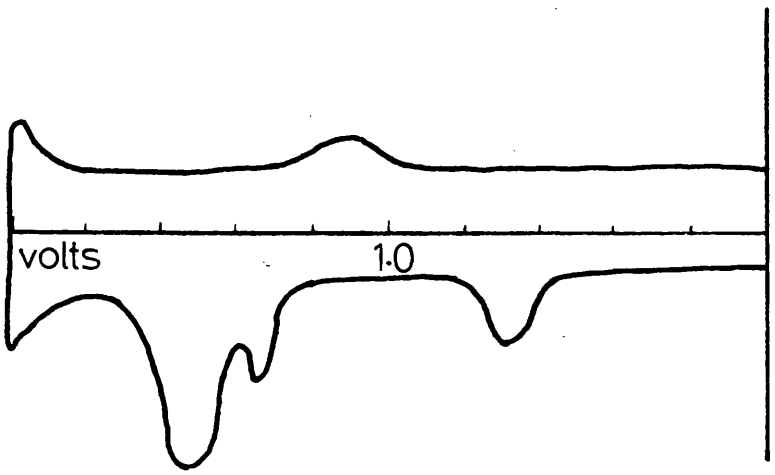
Bobbitt[65] has described a simple and versatile synthesis of 4-benzylisoquinolines. The benzylaminoacetal (201) was cyclised by boiling with 6N hydrochloric acid. The resultant 1,2-dihydroisoquinoline was trapped <u>in situ</u> with an excess of 3,4-dimethoxybenzaldehyde (150) resulting in the 4-benzylidene-1,4-dihydroisoquinoline salt (217). Treatment of this salt (217) with base effected a tautomeric change to give 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (218). This compound was isolated and purified as the methiodide salt (219) by treatment with iodomethane in acetone, and then reduced with sodium borohydride to give the tetrahydroisoquinoline (220). This compound was purified by column chromatography on basic alumina, eluting with ether.


OCH3
CH3O
CH3O
NH
OCH3
+
CHO
CH3O
CH3O
(201)
(150)
H+
OCH3
OCH3
CH3O
CH3O
N
base
NH
(218)
(217)
CH3I
NCH3
I-
NaBH4
NCH3
(219)
(220)

The cyclic voltammogram (figure 15) of (220) shows three oxidative peaks. The first, at a potential of + 0.7 volts corresponds to oxidation of the nitrogen lone pair of electrons. The second, at + 1.35 volts is due to ionisation of the dimethoxyphenyl ring, and the third, at + 1.5 volts is attributable to ionisation of the dimethoxyisoquinoline ring.

Figure 15

Cyclic Voltammogram of 2-Methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (220)



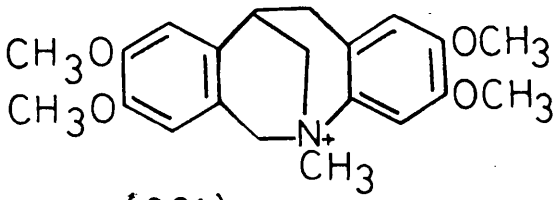
The substrate (220) was electrolysed at an anode potential of + 0.8 volts until the current had dropped to below 10mA and 2.2F.mol^{-1} of charge had been consumed. During the electrolysis the anolyte was stirred with anhydrous sodium carbonate to prevent the electrolyte from becoming acidic and inhibiting oxidation of the nitrogen lone pair of electrons by protonation. Work-up of the reaction gave a black solid which was found to be only partially soluble in acetone. The acetone-

insoluble material was collected and shown to be the methoperchlorate salt (221) coupled between the 6-position of the 3,4-dimethoxybenzyl substituent and the nitrogen atom in the tetrahydroisoquinoline ring. The ^{1}H n.m.r. spectrum of the product shows four singlet peaks in the aromatic region. The four methoxy groups and the N-methyl group give rise to five singlet peaks close together in the 3.6 - 3.9 ppm region. The non-equivalence of the two protons in the 1-position of the isoquinoline ring causes geminal coupling to occur and two one proton doublets are seen at 4.76 and 5.02 ppm each with a coupling constant of 14 Hz. A two proton doublet at 3.18 ppm of coupling constant 4Hz is attributable to the methylene group at the 3-position. A further two proton doublet at 3.37 ppm with a coupling constant of 2 Hz is due to the benzylic methylene group. The proton in the 4-position resonates at 4.08 ppm and is seen as a broad, poorly resolved peak due to coupling with the two adjacent methylene groups. Homonuclear decoupling experiments were carried out to aid interpretation of the spectrum. Irradiation at the frequency corresponding to 4.08 ppm caused the two doublets at 3.18 and 3.37 ppm to collapse to singlets, proving them both to be coupled to the proton in the 4-position. Irradiation at 3.18 ppm caused the signal at 4.08 ppm to become a triplet with a coupling constant of 2 Hz, corresponding to vicinal coupling with the two protons resonating at 3.37 ppm.

For this, and other tetrahydroisoquinoline derivatives, the ^{13}C n.m.r. spectrum was found to be of great value in confirming structures. For this compound there are five quartets in the aliphatic region due to the five methyl groups, and three triplets and one doublet corresponding to the three methylene groups and the one methyne group. In the aromatic region there are four singlets due to

the four carbon atoms at the points of ring fusion, and four doublets corresponding to the four atoms attached to the aromatic protons. There are also four singlet signals of greater chemical shift and these are due to the aromatic carbon atoms carrying the methoxy groups.

The mass spectrum has a base peak at (M-1) characteristic of a tetrahydroisoquinoline and there is also a major peak at (M-15) corresponding to loss of the methyl group from the nitrogen.



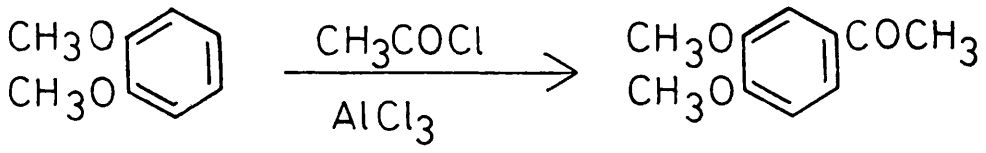
(221)

Miller's[64] results with laudanosine (101) demonstrated that the same reaction could be brought about by oxidation of the dimethoxyphenyl ring rather than by oxidation of the nitrogen lone pair of electrons. In the experiment described above the results for (103) and (220) show that an intramolecular coupling reaction is initiated by oxidation of the nitrogen lone pair, whereas ionisation of the dimethoxyphenyl ring in the salt (103) leads only to oxidation of the molecular skeleton without any coupling.

The first step in the synthesis of 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (233) was the cyclisation of the benzylaminoacetal (201) in hot hydrochloric acid in

the presence of 3,4-dimethoxyphenylglyoxal (225). The glyoxal was prepared by oxidation of 3,4-dimethoxybromacetophenone (224) which itself was obtained by the bromination of 3,4-dimethoxyacetophenone (222).

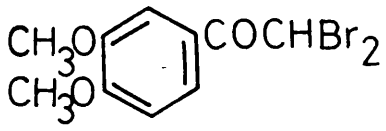
3,4-Dimethoxyacetophenone (222) was first[66] prepared in 62% yield by the Friedel-Crafts acylation of veratrole (136) with acetyl chloride in carbon disulphide. The use of benzene as solvent, however, is reported[67] to improve the reaction yield to 95%. Acetyl chloride was added dropwise to a mixture of aluminium chloride and veratrole (136) in dry benzene. Work-up of the reaction and vacuum distillation of the residual oil afforded 3,4-dimethoxyacetophenone (222) in 94% yield.



(136) (222)

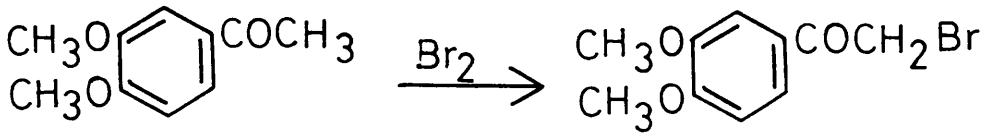
The original synthesis[68] of 3,4-dimethoxybromoacetophenone (224) by the treatment of 3,4-dimethoxyacetophenone with bromine in chloroform was attempted but a mixture of starting material (222), some product (224), and tar resulted. An orange crystalline precipitate was seen to form during the course of the preparation, but this disappeared before the reaction was complete. On a later occasion the orange solid was collected by terminating the reaction prematurely and it was shown to be 3,4-dimethoxydibromoacetophenone (223). This compound was unstable

and decomposed rapidly on exposure to moisture in the air with the evolution of hydrogen bromide fumes leaving a black tar, and this explains the problem encountered in the earlier preparation.



(223)

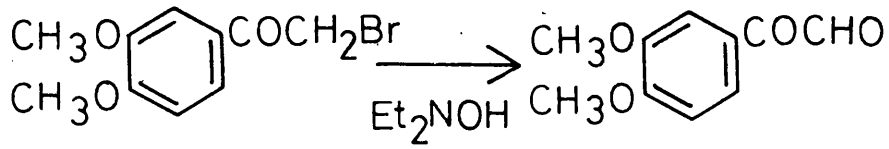
Fujii[67] reports similar difficulties experienced in the preparation of 3,4-dimethoxybromoacetophenone and states that the reaction yield can be considerably enhanced by the use of a solvent mixture of ether and chloroform (5:3) instead of chloroform alone. This preparation was followed and the required product (224) was formed in 91% yield.



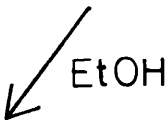
(222) (224)

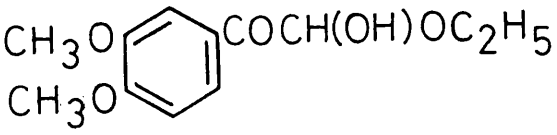
Treatment of 3,4-dimethoxybromoacetophenone (224) with selenium dioxide is reported[69] to bring about oxidation to the glyoxal (225) but a better method[70] is the use of N,N-diethylhydroxylamine as

oxidant. Thus a solution of the bromo compound (224) and N,N-diethylhydroxylamine in methanol was heated under reflux for 2.5 hours. The solvent was evaporated and the residue treated with ether to precipitate diethylamine hydrobromide which was removed by filtration. The filtrate was evaporated to leave 3,4-dimethoxyphenylglyoxal (225) as a red oil. The glyoxal is unstable and so it was treated with ethanol and isolated as the ethyl hemiacetal (226). The glyoxal can be regenerated from the hemiacetal as required simply by heating above the melting point.



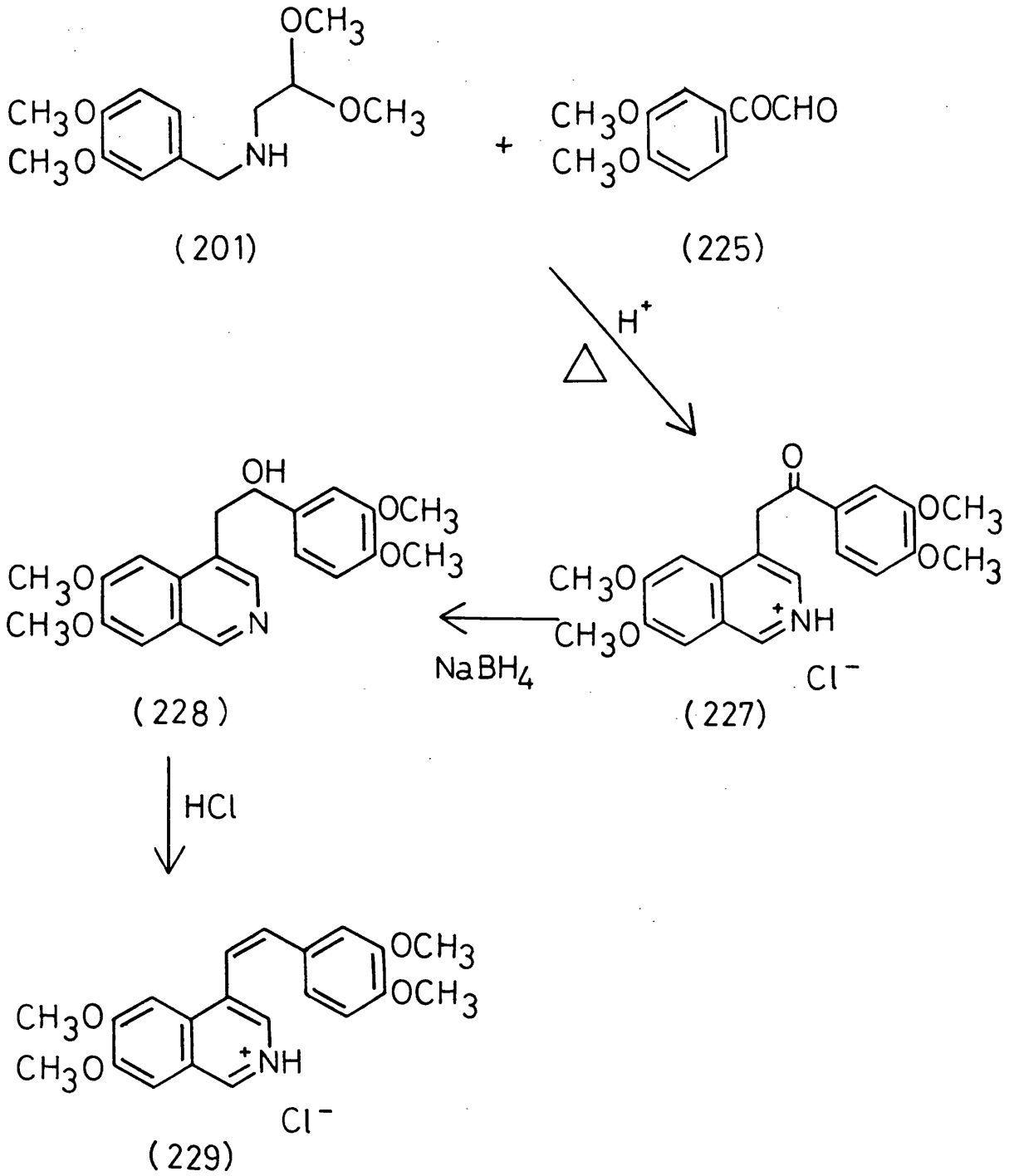
(224) (225)



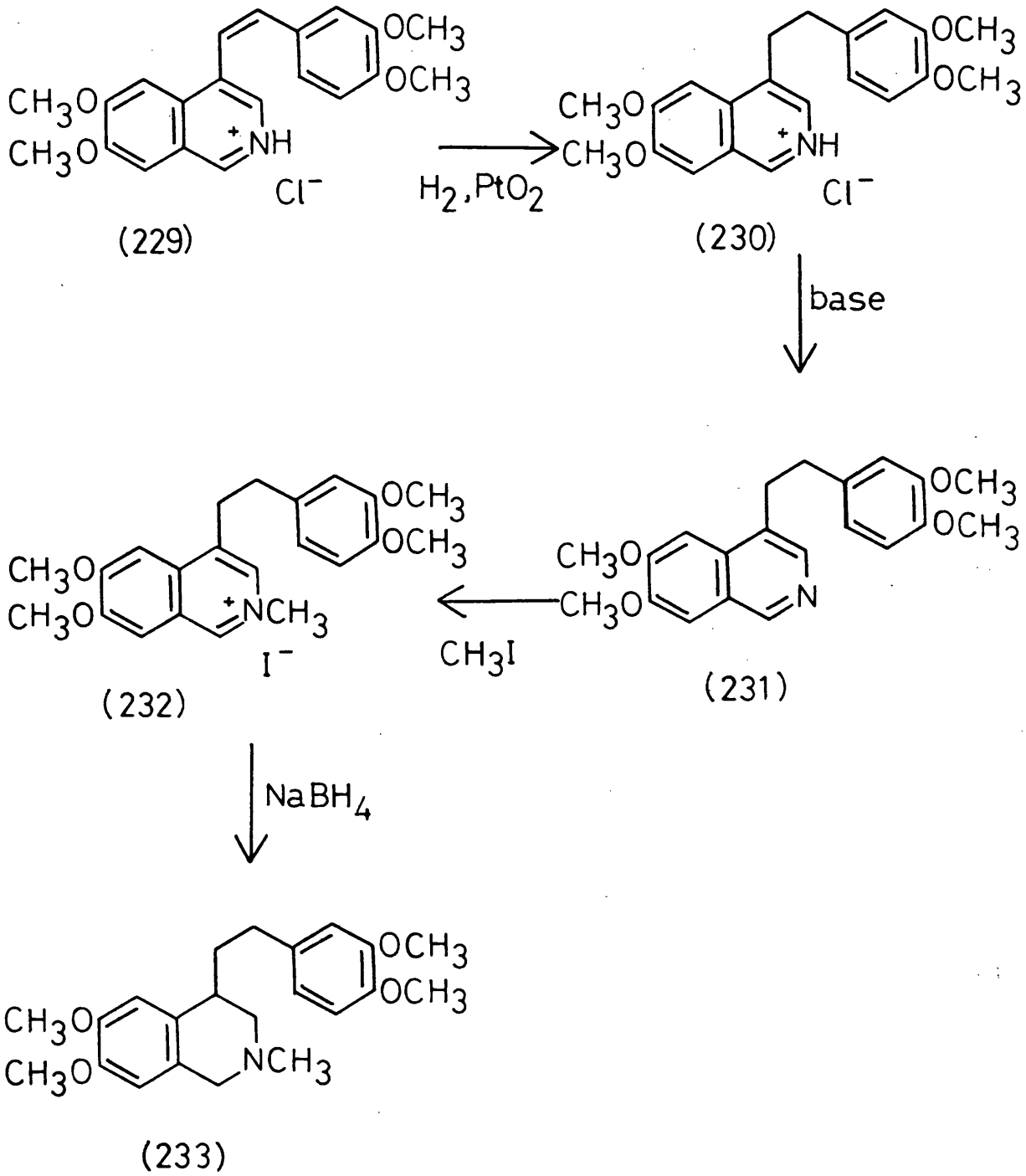


(226)

3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (201) was added to concentrated hydrochloric acid and warmed to 80°. The acetal was hydrolysed by the acid; it then cyclised and was dehydrated to give a reactive 1,2-dihydroisoquinoline. Molten 3,4-dimethoxyphenylglyoxal (225) was added to the reaction and this acted as an electrophile trapping the 1,2-dihydroisoquinoline and giving rise to 4-(3,4-dimethoxyphenacyl)-6,7-dimethoxyisoquinoline hydrochloride (227) after acid catalysed dehydration and tautomerism [69]. Reduction of this salt with sodium borohydride in ethanol gave the free base (228), and this was dissolved in chloroform and treated with hydrogen chloride to bring about dehydration giving 4-(3,4-dimethoxystyryl)-6,7-dimethoxyisoquinoline hydrochoride (229).


OCH3
CH3O
CH3O
OCH3
NH
(201)
+
CH3O
CH3O
COCHO
(225)
H+
△
OH
OCH3
OCH3
CH3O
CH3O
N
(228)
NaBH4
O
OCH3
OCH3
CH3O
CH3O
+NH
Cl−
(227)
HCl
OCH3
OCH3
CH3O
CH3O
+NH
Cl−
(229)

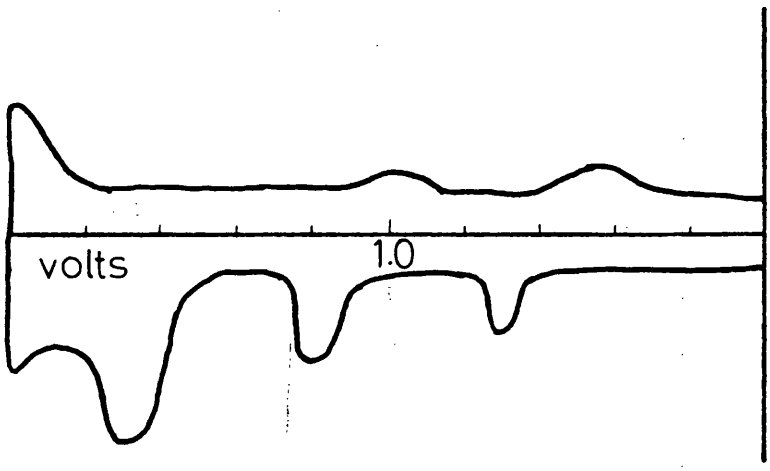
In the literature synthesis[71] of the 4-phenethyltetrahydroisoquinoline (233), the styrene hydrochloride (229) was converted to the perchlorate salt and was then hydrogenated. However, it was found that the hydrogenation step worked equally well with the hydrochloride salt (229). The salt was hydrogenated over Adams' catalyst to give 4-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoquinoline hydrochloride (230) in 90% yield. The free base (231) was obtained by basefication with ammonium hydroxide solution, and was then treated with iodomethane in acetone to form the methiodide salt (232). Reduction of this methiodide (232) with sodium borohydride in ethanol afforded the required base 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (233) as a colourless gum. The material could not be crystallised but was shown by thin layer chromatography (alumina/ether) to be pure.


OCH3
OCH3
CH3O
CH3O
NH
Cl−
H2,PtO2
(229)
(230)
base
CH3I
NCH3
I−
N
(231)
(232)
NaBH4
(233)

The cyclic voltammogram (figure 16) of (233) shows three oxidative peaks at potentials of + 0.75, 1.2 and 1.7 volts, corresponding to ionisation of the nitrogen lone pair of electrons, the dimethoxyphenyl ring, and the dimethoxyisoquinoline ring respectively. The substrate (233) was electrolysed at a potential of + 1.2 volts, and 4.1 $F.mol.^{-1}$ of charge was consumed. However, work-up of the anolyte gave a brown tar from which no products could be isolated. Electrolysis at a potential of + 0.8 volts, with the consumption of 1.7 $F.mol.^{-1}$ of charge, also gave a tarry residue. In both of these experiments the anolyte was stirred with sodium carbonate to prevent the electrolyte from becoming acidic.

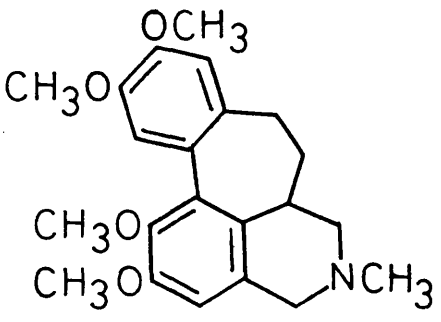
Figure 16

Cyclic Voltammogram of 2-Methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (233)



The last experiment to be carried out in this thesis was the oxidation of 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-

tetrahydroisoquinoline (233) with thallium (III) trifluoroacetate[72]. The substrate (233) was added to thallium trifluoroacetate in a mixture of acetonitrile and carbon tetrachloride at -40° under nitrogen and in the absence of light[48], followed by boron trifluoride etherate. A slurry of dry ice in acetonitrile provided the appropriate temperature conditions for the reaction[73], and the addition of boron trifluoride etherate is essential for oxidations of this type carried out in carbon tetrachloride or acetonitrile[74]. The reaction mixture was partially evaporated and the residue treated with ammonium hydroxide solution. The organic material was extracted with chloroform, and the extract evaporated to leave a brown solid. Thin layer chromatography (alumina/ether) showed that all the starting material had been consumed and that there was one component of higher R_f value in addition to intractable baseline material. A short basic alumina column, eluted with ether, served to isolate a compound which was shown to be the tetracycle (234) formed by a coupling reaction between the 4-position of the tetrahydroisoquinoline ring and the 6-position of the dimethoxyphenyl ring.

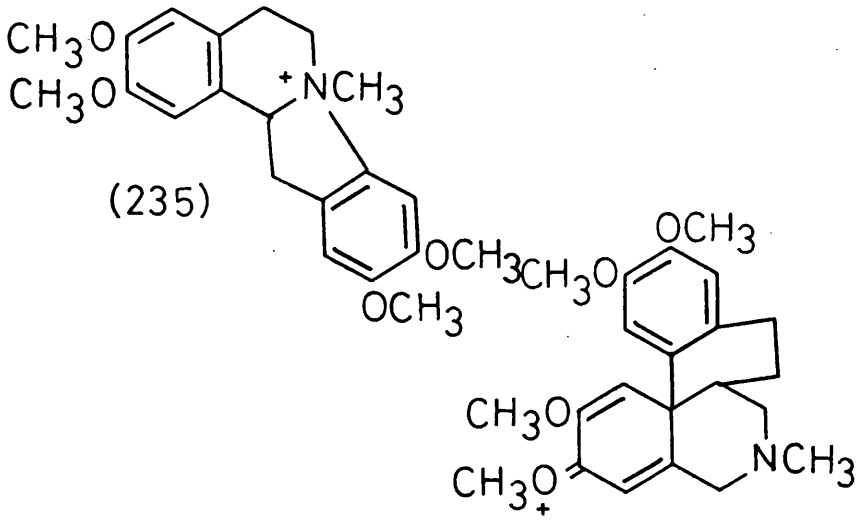


(234)

The ^{1}H n.m.r. spectrum of this compound exhibited three one proton singlets in the aromatic region. The aliphatic portion of the spectrum was less clearly defined. The ^{13}C n.m.r. spectrum showed the presence of five aliphatic methyl groups, four methylene groups, and one methyne carbon atom. The aromatic region showed three doublets corresponding to the carbon atoms in the 2- and 5-positions of the dimethoxyphenyl ring and the 8-position of the isoquinoline ring. The mass spectrum of the product was characteristic of a tetrahydroisoquinoline with a major fragmentation peak corresponding to the facile loss of one hydrogen atom from the molecule

These results may again be interpreted in terms of the Baldwin rules, for the formation of O-methylflavinantine (102) rather than the salt (235) may be viewed as the operation of a 6-Endo-Trig as opposed to a 5-Endo-Trig process. However, with the 1-phenethylisoquinoline derivative (105) the salt (106) is formed as the major product via a 6-Endo-Trig process.

In the 4-benzyl series formation of the cation (221) can be considered as a 6-Endo-Trig process. The homologue (233) on the other hand does not form a salt although it could have done through a favoured 7-Endo-Trig transition state. Instead it gives rise to the homoisoaporphine (234). Here it seems possible that the initial product of reaction is the intermediate (236) which, through rearrangement, affords the homoisoaporphine (234). If this is so, then initial reaction is again of the ubiquitous 6-Endo-Trig type.



(235)

(236)

EXPERIMENTAL

Superdry Acetonitrile

Acetonitrile was distilled twice from phosphorus pentoxide (5 $g.dm^{-3}$) and allowed to stand over 3A molecular sieves (activated at 250° for 24 hours) for one week, and then decanted onto fresh activated sieves (50 $g.dm^{-3}$) for a further 24 hours.

3,3',4,4'-Tetramethoxydeoxybenzoin (143)

3,4-Dimethoxyphenylacetic acid (20 g, 0.1 mol) was heated under reflux with freshly distilled thionyl chloride (10 cm^3) in dry benzene (100 cm^3) for 4 hours. Removal of the solvent under reduced pressure gave 3,4-dimethoxyphenylacetyl chloride (142) as a red oil (22 g, 100%) which was used immediately.

Aluminium chloride (14.7 g, 0.11 mol) was added portionwise to a solution of veratrole (136, 14.15 g, 0.1 mol) in dry dichloromethane (50 cm^3). Then was added dropwise a solution of 3,4-dimethoxyphenylacetyl chloride (142, 22 g, 0.1 mol) in dry dichloromethane (20 cm^3). The reaction mixture was heated under reflux for 3 hours and then cooled and poured onto ice (300 g). After acidification with concentrated hydrochloric acid (50 cm^3) the mixture was extracted with dichloromethane (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a solid which was recrystallised twice from ethanol to give the product (143) as pale yellow crystals (24 g, 74%) m.p. 108°.

$\bar{\nu}$ max (cm^{-1}) : 1675 (C=O)

λ max (nm (log ε)) : 209 (4.33), 243 (4.29), 281 (4.03), 311 (3.88)

δ (ppm, $CDCl_3$) : 3.8 - 4.0 (12H, 4s, 4 x OCH_3), 4.18 (2H, s, CH_2), 6.8 - 7.8 (6H, complex, aromatics)

m/e : 316 (M^+), 179 ($ArCOCH_2$), 165 (ArCO), 151 ($ArCH_2$)

Metastable M^* at 86.2 (316 → 165)

Attempted Wolff-Kishner reduction of (143)

A mixture of 3,3',4,4'-tetramethoxydeoxybenzoin (143, 15.8 g, 0.05 mol), 95% hydrazine (12 cm^3) and potassium hydroxide (20 g) was heated under reflux in diethylene glycol (200 cm^3) for 4 hours. The solution was cooled, poured into water (600 cm^3) and extracted with ether (3 x 200 cm^3) to return the starting material (143) unchanged.

1,2-Bis(3,4-dimethoxyphenyl)ethanol (141)

3,3',4,4'-Tetramethoxydeoxybenzoin (143, 0.5 g, 1.6 mmol) was stirred for 4 days with sodium borohydride (0.4 g) in ethanol (100 cm^3). The solvent was evaporated under reduced pressure and the residue treated with water (200 cm^3) and extracted with chloroform (3 x 100 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a white powder (0.43 g, 85%) m.p. 79°.

$\bar{\nu}$ max (cm^{-1}) : 3520 (O-H)

λ max (nm(log ε)) : 211 (4.43), 234 (4.22), 284 (3.77)

δ (ppm, $CDCl_3$) : 2.06 (1H, s, OH, removed by deuteration) 2.96 (2H, d, CH_2, J = 7H_z), 3.84 (12H, 2s, 4 x OCH_3), 4.82 (1H, t, CH, J = 7H_z) 6.7 - 7.0 (6H, complex, aromatics).

m/e : 318 (M^+), 300 ($M-H_2O$)

3,3',4,4'-Tetramethoxystilbene (137)

1,2-Bis(3,4-dimethoxyphenyl) ethanol (141, 0.2 g, 0.63 mmol) was heated under reflux in glacial acetic acid (2 cm^3) for 3 hours and then cooled and diluted with water (4 cm^3). The solid was collected by filtration and recrystallised from methanol as fine white needles (0.18 g, 95%) m.p. 134°.

$\bar{\nu}$ max (cm^{-1}) : 950 (trans CH=CH)

λ max (nm (log ε)) : 214 (4.27), 238 (4.15), 339 (4.37)

δ (ppm, $CDCl_3$) : 3.90 (12H, s, 4 x $O\underline{CH}_3$), 6.8 - 7.1 (8H, complex, aromatics and $\underline{CH}=\underline{CH}$)

$\underline{m/e}$: 300 ($M^{\cdot+}$), 285 ($M-CH_3$)

3,3',4,4'-Tetramethoxybibenzyl (1)

3,3',4,4'-Tetramethoxystilbene (137, 3.0 g, 0.01 mol) was dissolved in ethanol (300 cm^3) and hydrogenated (2 atm.) for 24 hours with 10% palladium on carbon (0.1 g) as catalyst. Filtration and removal of the solvent under reduced pressure, followed by recrystallation from methanol gave the product (1) as white rods (2.85 g, 94%) m.p. 107° (lit.[2] m.p. 109-110°).

$\bar{\nu}$ max (cm^{-1}) : 1400 (aromatic ether)

λ max (nm (log ε)) : 210 (4.39), 234 (4.13), 285 (3.68)

δ (ppm, $CDCl_3$) : 2.82 (4H, s, $\underline{CH}_2\underline{CH}_2$), 3.80 (12H, 2s, 4 x $O\underline{CH}_3$), 6.6 - 6.8 (6H, complex, aromatics)

$\underline{m/e}$: 302 ($M^{\cdot+}$), 151 ($ArCH_2$)

Anodic oxidation of 3,3',4,4'-tetramethoxybibenzyl (1)

(a) 3,3',4,4'-Tetramethoxybibenzyl (I, 1.0 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (150 cm^3) and electrolysed

at a carbon felt anode at a potential of + 1.5 volts until the current dropped to 10 mA. The anolyte was partially evaporated under reduced pressure and the residue added to water (150 cm^3) and then extracted with dichloromethane (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a black solid which was chromatographed on silica, eluting with 50% ether in hexane to remove the tarry impurities. Evaporation of the eluate under reduced pressure gave a white solid.

$^m/_e$: 302 ($M^{+\cdot}$, bibenzyl (1)) and 298 ($M^{+\cdot}$, phenanthrene (3)).

(b) The electrolysis was repeated using 0.1 M sodium perchlorate in superdry acetonitrile containing deuterium oxide (0.01 $mol.dm^{-3}$) as electrolyte. The results were identical to those given above.

3,4-Dimethoxycinnamic acid (152)

Malonic acid (151, 25 g, 0.25 mol) and 3,4-dimethoxybenzaldehyde (150, 20 g, 0.12 mol) were dissolved in pyridine (50 cm^3) by warming to 50°. Piperidine (2 cm^3) was added and the mixture maintained at 80-85° for 1 hour and then heated under reflux for 3 hours. The cooled solution was poured into water (500 cm^3) and acidified with concentrated hydrochloric acid (65 cm^3). The crude precipitate was collected by filtration, washed with water (4 x 20 cm^3) and then dissolved in 1 M sodium hydroxide solution (350 cm^3). The solution was filtered, diluted with water (150 cm^3) and acidified with 50% hydrochloric acid (75 cm^3). The solid was collected by filtration, washed with water (4 x 20 cm^3) and dried *in vacuo* at 60° to give a white powder (22 g, 89%) m.p. 181°.

$\bar{\nu}$ max (cm^{-1}) : 3100-3400 (O-H), 1680 (C=O)

λ max (nm (log ε)) : 209 (4.00), 220 (4.06), 237 (4.05), 299 (4.08), 325 (4.14)

δ (ppm, DMSO) : 3.89 (6H, s, 2 x $OC\underline{H}_3$), 6.30 (1H, d, $C\underline{H}$=CH, $\underline{J}$ = $16H_z$), 6.8 - 7.2 (3H, complex, aromatics), 7.60 (1H, d, CH=$C\underline{H}$, $\underline{J}$ = $16H_z$)

$\underline{m/e}$: 208 ($M^{+\cdot}$), 193 (m-CH_3)

Metastable M^* at 179.1 (208 → 193)

3,4-Dimethoxyphenylpropanoic acid (153)

3,4-Dimethoxycinnamic acid (152, 10.4 g, 0.05 mol) was dissolved in ethanol (250 cm^3) and hydrogenated (4 atm.) for 24 hours with platinum oxide (0.1 g) as catalyst. Filtration and removal of the solvent under reduced pressure gave a white solid which was recrystallised from water as fine white needles (9.6 g, 91%) m.p. 74°.

$\bar{\nu}$ max (cm^{-1}) : 3430 (O-H), 1690 (C=O)

λ max (nm (log ε)) : 208 (4.33), 232 (3.99), 283 (3.53)

δ (ppm, $CDCl_3$) : 2.66 (2H, t, $C\underline{H}_2CH_2$, $\underline{J}$ = $7H_z$), 2.92 (2H, t, $CH_2C\underline{H}_2$, $\underline{J}$ = $7H_z$), 3.84 (6H, s, 2 x $OC\underline{H}_3$), 6.6 - 6.8 (3H, complex, aromatics), 9.0 - 9.8 (1H, broad s, COO$\underline{H}$, removed by deuteration).

$\underline{m/e}$: 210 ($M^{+\cdot}$), 195 (M-CH_3), 165 ($ArCH_2CH_2$), 151 ($ArCH_2$)

3,4-Dimethoxyphenylpropanoyl choride (149)

3,4-Dimethoxyphenylpropanoic acid (153, 15 g, 0.071 mol) was heated under reflux for 0.5 hours in dry toluene (100 cm^3) with freshly distilled thionyl chloride (30 cm^3). The solvent was removed under reduced pressure to leave a red oil (16 g, 98%) which was used immediately.

3-(3,4-Dimethoxyphenylpropanoyl) indole (74)

To dry magnesium turnings (1.8 g, 0.074 mol) and a crystal of iodine in dry ether (10 cm^3) was added bromoethane (7.75 g, 5.3 cm^3, 0.071 mol) in dry ether (15 cm^3). To this was added a solution of indole (13, 9.0 g, 0.076 mol) in dry ether (30 cm^3) at such a rate as to maintain gentle boiling. The solution was stirred for 10 minutes and then homogenised by the addition of dry dichloromethane (15 cm^3).

The Grignard reagent (41) was added dropwise to a solution of 3,4-dimethoxyphenylpropanoyl chloride (149, 16 g, 0.071 mol) in dry ether (50 cm^3). The mixture was stirred at room temperature for 2 days and then hydrolysed with 2N hydrochloric acid (300 cm^3) and extracted with chloroform (3 x 200 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a viscous red oil which was dissolved in hot propan-2-ol (20 cm^3). On cooling a pink solid was obtained which was recrystallised from propan-2-ol as pale pink needles (7.2 g, 34%) m.p. 171°.

$\bar{\nu}$ max (cm^{-1}) : 3190 (N-H), 1610 (C=O)

λ max (nm (log ε)) : 213 (4.42), 242 (4.13), 260 (3.92), 293 (3.99), 303 (4.00)

δ (ppm, DMSO) : 2.8 - 3.2 (4H, 2t, $C\underline{H}_2C\underline{H}_2$, $\underline{J}$ = $7H_3$), 3.71 (3H, s, $OC\underline{H}_3$), 3.74 (3H, s, $OC\underline{H}_3$), 6.8 - 7.6 (6H, complex, aromatics), 8.1 - 8.3 (1H, dd, $C_4\underline{H}$), 8.34 (1H, d, $C_2\underline{H}$, $\underline{J}$ = $3H_2$), 11.8 (1H, broad, N$\underline{H}$, removed by deuteration)

$\underline{m/e}$: 309 ($M^{+\cdot}$), 151 ($ArCH_2$), 144 (indole CO), 117 (indole)

Metastables M^* at 93.4 (144 → 117) and 67.1 (309 → 144)

Anodic oxidation of 3-(3,4-dimethoxyphenylpropanoyl) indole (74)

The substrate (74, 1.0 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (150 cm^3) and electrolysed at an anode potential of + 1.1 - 1.2 volts until the current dropped to 5 mA. The anolyte was partially evaporated under reduced pressure and then added to water (300 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a dark red solid which was recrystallised twice from ethanol as dark red rods (0.52 g, 64%) m.p. 228° (lit.[10] m.p. 230-240°).

$\bar{\nu}$ max (cm^{-1}) : 3340, 1670, 1660, 1640

λ max (nm) : 215, 241, 310, 350

δ (ppm, DMSO) : 2.96 (4H, s, $C\underline{H}_2C\underline{H}_2$), 6.58 (1H, s), 6.80 (1H, s), 7.2 - 7.8 (3H, complex, aromatics), 7.98 (1H, dd, $C_4\underline{H}$), 12.60 (1H, broad, removed by deuteration).

$\underline{m/e}$: 277 ($M^{+\cdot}$)

This compound was light sensitive and decomposed on standing. Decomposition was noticeably faster if the compound was subjected to column chromatography.

1-Benzenesulphonylindole (157)

Potassium hydroxide (22.5 g, 0.4 mol) was dissolved in dry dimethylsulphoxide (200 cm^3) under nitrogen. Indole (13, 11.7 g, 0.1 mol) was added and the solution stirred for 3 hours to form the indole anion (51). The solution was cooled on ice and benzenesulphonyl chloride (35 g, 26 cm^3, 0.2 mol) was added dropwise. The reaction mixture was stirred for 1 hour and then water (450 cm^3) was added

cautiously. The precipitate was collected by filtration and recrystallised from methanol as colourless rods (20.3 g, 79%) m.p. 77° (lit.[13] m.p. 77.5 - 79°).

$\bar{\nu}$ max (cm^{-1}) : 1130 (S=O)

λ max (nm (log ε)) : 214 (4.40), 2 53 (4.12), 286 (3.48), 293 (3.44)

δ (ppm, $CDCl_3$) : 6.53 (1H, d, $C_3\underline{H}$, $\underline{J}$ = $4H_3$), 7.0 - 8.1 (10H, complex, aromatics)

$\underline{m/e}$: 257 ($M^{+\cdot}$), 141 ($PhSO_2$), 116 ($M-PhSO_2$)

Attempted preparation of 1-benzenesulphonyl(-2-(3,4-dimethoxyphenyl-propanoyl)indole

(a) Benzenesulphonylindole (157, 15 g, 0.06 mol) was dissolved in dry ether (200 cm^3) under nitrogen. To it was added 1.6 M n-butyllithium in hexane (44 cm^3, 0.07 mol), and the mixture heated under reflux for 7 hours. The solution was cooled and 3,4-dimethoxy-phenylpropanoyl chloride (149, 16 g, 0.07 mol) in dry ether (200 cm^3) was added dropwise. The mixture was stirred overnight at room temperature and then filtered to remove the precipitated inorganic salts. The filtrate was washed with water (2 x 100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a red oil to which was added methanol (30 cm^3). The precipitate was collected by filtration and recrystallised from methanol as off-white rods (2 g, 20%) m.p. 122°.

$\bar{\nu}$ max (cm^{-1}) : 1140 (S=O)

λ max (nm (log ε)) : 210 (4.12), 225 (4.27), 264 (3.25), 270 (3.36), 277 (3.29)

δ (ppm, $CDCl_3$) : 0.84 (3H, t, $C\underline{H}_3$, $\underline{J}$ = $5H_3$), 1.60 (2H, complex,

$C\underline{H}_2CH_3$), 2.10 (2H, complex, $CHC\underline{H}_2$), 4.40 (1H, t, $C\underline{H}$, $\underline{J}$ = 6Hz), 7.4 - 7.8 (10H, complex, aromatics)

δ (ppm, DMSO) : 13.43 (q, $\underline{C}H_3$), 20.31 (t, $\underline{C}H_2CH_3$), 27.14 (t, $CH\underline{C}H_2$), 80.67 (d, $\underline{C}H$), 128.99 (d), 129.10 (d), 134.46 (d), 138.14 (s)

$\underline{m/e}$: 338 (M^+), 309 (M-Et), 297 (M-Pr), 197 (M-$PhSO_2$), 141 ($PhSO_2$)

Found : C, 56.85; H, 5.4; S, 18.8.

$C_{16}H_{18}O_4S_2$ requires : C, 56.8; H, 5.4; S, 18.95%.

(b) Benzenesulphonylindole (154, 1.16 g, 4.76 mmol) was dissolved in dry tetrahydrofuran (35 cm^3) and cooled to -78° under nitrogen. To this was added 1.6 M n-butyllithium in hexane (5 cm^3, 8 mmol). The solution was allowed to warm to room temperature and then re-cooled to -78°. 3,4-Dimethoxyphenylpropanoyl chloride (149, 1.05 g, 4.76 mmol) in dry tetrahydrofuran (10 cm^3) was added and the mixture stirred at room temperature for one hour and then poured into water (200 cm^3) and extracted with ether (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure yielded an intractable red gum.

(c) The reaction above (b) was repeated using freshly distilled (b.p. 166°, 0.7 mm Hg) 3,4-dimethoxyphenylpropanoyl chloride (149).

$\underline{m/e}$: 228 (M^+), 192 (M-HCl), 151 ($ArCH_2$)

The result was the same as in (b).

(d) Benzenesulphonylindole (154, 1.16 g, 4.76 mmol) in dry tetrahydrofuran (35 cm^3) was cooled to -78° under nitrogen and treated with butyllithium (5 cm^3) as above.

The acid chloride (149, 1.05 g, 4.76 mmol) in dry tetrahydrofuran

($50\ cm^3$) was cooled to -78^o under nitrogen and to it was added the solution of 2-lithiobenzenesulphonylindole (160) prepared above. The reaction was worked-up in the usual way to give an orange oil. Column chromatography on silica eluting with 50% dichloromethane in petroleum ether gave benzenesulphonylindole (154, 0.65 g, 56%). No other product was obtained.

(e) 2-Lithiobenzenesulphonylindole (160) was prepared as above and to it was added methyl 3,4-dimethoxyphenylpropanoate (159, 1.06 g, 4.76 mmol). Work-up gave an intractable orange oil.

Methyl 3,4-dimethoxyphenylpropanoate (159)

3,4-Dimethoxyphenylpropanoic acid (153, 12 g, 0.057 mol) was dissolved in Analar methanol ($25\ cm^3$) and to it was added concentrated sulphuric acid ($5\ cm^3$). The mixture was stirred at room temperature for 3 days and then neutralised with saturated sodium bicarbonate solution and extracted with ether ($3 \times 100\ cm^3$). The combined organic phases were washed with water ($100\ cm^3$) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a solid which was recrystallised from methanol as colourless rods (12.13 g, 95%) m.p. 30^o.

$\bar{\nu}$ max (cm^{-1}) : 1730 (C=O)

λ max (nm (log ε)) : 210 (4.09), 233 (3.90), 285 (3.46)

δ (ppm, $CDCl_3$) : 2.5 - 3.0 (4H, complex, $C\underline{H}_2C\underline{H}_2$), 3.64 (3H, s, $C\underline{H}_3$), 3.84 (6H, 2s, 2 x $OC\underline{H}_3$), 6.76 (3H, complex, aromatics)

$\underline{m/e}$: 224 ($M^{+\cdot}$), 209 ($M-CH_3$), 151 ($ArCH_2$)

1-Benzenesulphonylindole-2-carboxylic acid (161)

Benzenesulphonylindole (154, 2.57 g, 0.01 mol) was dissolved in dry tetrahydrofuran (80 cm^3) under nitrogen and cooled to -78°. 1.6 M n-Butyllithium in hexane (6.7 cm^3, 0.011 mol) was added and the mixture allowed to warm to room temperature and then poured onto a slurry of solid carbon dioxide in dry ether (100 cm^3). The mixture was acidified with 2N hydrochloric acid (200 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a white solid which was recrystallised from dichloromethane as white cubes (2.77 g, 92%) m.p. 161°.

$\bar{\nu}$ max (cm^{-1}) : 3200-2500 (O-H), 1710 (C=O)

λ max (nm (log ε)) : 217 (4.35), 270 (4.22)

δ (ppm, DMSO) : 7.2 - 8.2 (complex)

m/e : 301 ($M^{\cdot+}$), 257 ($M-CO_2$)

Attempted preparation of 1-benzenesulphonylindole-2-aldehyde

(a) Benzenesulphonylindole (154, 5 g, 0.02 mol) was dissolved in dry tetrahydrofuran (20 cm^3) under nitrogen and then was added 1.6 M n-butyllithium in hexane (15 cm^3, 0.024 mol) at such a rate that gentle boiling was maintained. The solution was cooled to 5° and N-methylformanilide (2.7 g, 2.5 cm^3, 0.02 mol) in dry ether (7 cm^3) was added. The mixture was heated under reflux for 3 hours and then poured onto ice (10 g), acidified with 2N hydrochloric acid (25 cm^3) and extracted with ether (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a dark

red tar which failed to yield any products.

(b) The above reaction was repeated, but the reaction mixture was stirred at room temperature of 0.5 hours and not heated. Work-up again gave an intractable tar.

1-Methylindole-2-aldehyde (162)

To 1-methylindole (5 g, 4.9 cm^3, 0.038 mol) in dry ether (20 cm^3) under nitrogen was added 1.6 M n-butyllithium in hexane (28.5 cm^3, 0.046 mol) and the mixture heated under reflux for 2 hours. The solution was cooled to 5^o and N-methylformanilide (5.15 g, 4.7 cm^3, 0.038 mol) in dry ether (15 cm^3) was added. The reaction mixture was heated under reflux for 3 hours and then cooled, poured onto ice (20 g). acidified with 2N hydrochloric acid (40 cm^3) and extracted with ether (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a red oil which was subjected to column chromatography on silica, eluting with 30% dichloromethane in petroleum ether. The first fractions contained 1-methylindole (1.43 g, 28.6%). The required product (162) was obtained by evaporation of the middle fractions followed by recrystallisation from petroleum ether as yellow needles (0.18 g, 3%) m.p. 65^o.

$\bar{\nu}$ max (cm^{-1}) : 1670 (C=O)

λ max (nm (log ε)) : 208 (4.11), 236 (4.07), 313 (4.18)

δ (ppm, $CDCl_3$) : 4.04 (3H, s, $\underline{CH}_3$), 7.0 - 7.8 (5H. complex, aromatics), 9.88 (1H, s, $\underline{CH}O$)

$\underline{m/e}$: 159 ($M^{\cdot+}$), 130 (M-CHO)

Metastable M^* at 106.3 (159 → 130)

Evaporation of the final fractions and recrystallisation from petroleum

ether gave 1-methyl-2-(1-hydroxypentyl)indole (163) as colourless needles (0.09 g, 1.5%) m.p. 105°.

$\bar{\nu}$ max (cm^{-1}) : 3250 (O-H)

λ max (nm (log ε)) : 226 (4.46), 281 (3.90), 288 (3.91)

δ (ppm, $CDCl_3$) : 0.90 (3H, t, $CH_2\underline{CH_3}$, $\underline{J}$ = 6Hz), 1.40 (4H, complex, $\underline{CH_2}\underline{CH_2}$), 1.68 (1H, s, $\underline{OH}$, removed by deuteration), 1.8 - 2.0 (2H, complex, $CH\underline{CH_2}$), 3.73 (3H, s, $N\underline{CH_3}$), 4.76 (1H, t, $\underline{CH}$, $\underline{J}$ = 7Hz), 6.38 (1H, s, $C_3\underline{H}$), 6.9 - 7.7 (4H, complex, aromatics)

δ (ppm, $CDCl_3$) : 13.98 (q, $CH_2\underline{CH_3}$), 22.59 (t), 28.33 (t), 30.07 (t), 36.13 (q, $N\underline{CH_3}$), 67.45 (d, $\underline{CH}$), 99.03 (d), 109.11 (d), 119.56 (d), 120.70 (d), 127.31 (s), 139.57 (s), 142.21 (s)

$\underline{m/e}$: 217 (M^+), 199 ($M-H_2O$), 184 ($M-H_2O-CH_3$), 170 ($M-H_2O-Et$)

Found : C, 77.3; H, 8.8; N, 6.3.

$C_{14}H_{19}NO$ requires : C, 77.4; H, 8.8; N, 6.4%.

Potassium ethyl 2-nitrophenylpyruvate (166)

To freshly cut potassium (19.6 g, 0.5 mol) in dry ether (150 cm^3) under nitrogen was added dropwise absolute ethanol (125 cm^3) and dry ether (100 cm^3) at such a rate as to maintain steady boiling. When the potassium had dissolved the solution was cooled and diluted with dry ether (1.25 dm^3). Diethyl oxalate (73 g, 67.8 cm^3. 0.5 mol) was added followed after 10 minutes by 2-nitrotoluene (68.5 g, 58.9 cm^3, 0.5 mol). The mixture was stirred at room temperature for 3 days and then the precipitated purple crystals collected by filtration and washed with dry ether (105 g, 76%).

2-Ethoxycarbonylindole (165)

Potassium ethyl 2-nitrophenylpyruvate (166, 30 g, 0.11 mol) was dissolved in glacial acetic acid (200 cm^3) and hydrogenated (2 atm) for 20 hours with 5% palladium on carbon (0.2 g) as catalyst. The solution was filtered and diluted with water (3 dm^3). The precipitate was collected by filtration, washed with water (5 x 100 cm^3) and recrystallised twice from methanol to give white rods (13.3 g, 64%) m.p. 123° (lit.[21] m.p. 118-124°).

$\bar{\nu}$ max (cm^{-1}) : 3320 (N-H), 1685 (C=O)

λ max (nm (log ε)) : 208 (4.29), 222 (4.32), 299 (4.26)

δ (ppm, $CDCl_3$) : 1.40 (3H, t, $\underline{CH}_3$, $\underline{J}$ = $8H_z$), 4.40 (2H, q, $\underline{CH}_2$, $\underline{J}$ = $8H_z$), 7.0 - 7.8 (5H, complex, aromatics), 9.36 (1H, broad, N$\underline{H}$, removed by deuteration)

$\underline{m/e}$: 189 ($M^{+\cdot}$), 174 (M-CH_3), 161 (M-Et)

Methyl 3,4-dimethoxyphenylacetate (167)

3,4-Dimethoxyphenylacetic acid (39.2 g, 0.2 mol) was dissolved in warm Analar methanol (25 cm^3) and to it was added concentrated sulphuric acid (5 cm^3). The mixture was heated under reflux for 2 hours. The cooled solution was added to water (200 cm^3), basefied with 2N ammonium hydroxide solution and extracted with ether (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure followed by vacuum distillation gave the ester (167) as a colourless oil (37 g, 88%) b.p. 192° (0.7 mm Hg).

$\bar{\nu}$ max (cm^{-1}) : 1735 (C=O)

λ max (nm (log ε)) : 210 (4.10), 234 (3.86), 284 (3.43)

δ (ppm, $CDCl_3$) : 3.56 (2H, s, $C\underline{H}_2$), 3.66 (3H, s, $C\underline{H}_3$), 3.86 (6H, s, 2 x $OC\underline{H}_3$), 6.83 (3H, complex, aromatics)

$\underline{m/e}$: 210 ($M^{+\cdot}$), 195 ($M-CH_3$), 151 ($ArCH_2$)

2-(3,4-Dimethoxyphenyl)ethanol (168)

A solution of methyl 3,4-dimethoxyphenylacetate (167, 30 g, 0.14 mol) in dry ether (120 cm^3) was added dropwise to a slurry of lithium aluminium hydride (6 g) in dry ether (300 cm^3). The mixture was heated under reflux for 1 hour and then cooled. Excess hydride was decomposed by the cautious addition of water. The inorganic salts were removed by filtration and washed with ether. The filtrate was dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure left an oil which gave a pure white solid on standing (24.7 g, 97%) m.p. 44°.

$\bar{\nu}$ max (cm^{-1}) : 3300 (O-H)

λ max (nm (log ε)) : 208 (4.08), 231 (3.86), 283 (3.44)

δ (ppm, $CDCl_3$) : 1.88 (1H, s, O$\underline{H}$, removed by deuteration), 2.76 (2H, t, $C\underline{H}_2OH$, $\underline{J}$ = 6Hz), 3.76 (2H, t, $C\underline{H}_2CH_2$, $\underline{J}$ = 6Hz), 3.79 (3H, s, $OC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 6.70 (3H, complex, aromatics)

$\underline{m/e}$: 182 ($M^{+\cdot}$), 165 (M-OH), 151 ($ArCH_2$), 137 (Ar)

2-(3,4-Dimethoxyphenyl)bromoethane (169)

2-(3,4-Dimethoxyphenyl)ethanol (168, 15 g, 0.08 mol) was dissolved in dry ether (900 cm^3) and to it was added freshly distilled phosphorus tribromide (15 cm^3). The mixture was allowed to stand overnight at room temperature, and then washed with water (100 cm^3) and saturated

aqueous sodium bicarbonate (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an oil which solidified on standing and was recrystallised as white rods from ethanol (9.6 g, 49%) m.p. 51°.

$\bar{\nu}$ max (cm^{-1}) : 1135 (aromatic ether)

λ max (nm (log ε)) : 211 (4.19), 236 (3.95), 284 (3.49)

δ (ppm, $CDCl_3$) : 2.8 - 3.6 (4H, complex, $C\underline{H}_2C\underline{H}_2$), 3.88 (6H, 2s, 2 x $OC\underline{H}_3$), 6.8 - 7.0 (3H, complex, aromatics)

$\underline{m/e}$: 246/244 (M^+), 231/229 ($M-CH_3$), 165 (M-Br), 151 ($ArCH_2$)

Metastable M^* at 92.7 (246 → 151)

Attempted preparation of 3,4-dimethoxyphenethyl magnesium bromide (164)

(a) To dried magnesium turnings (0.92 g, 0.038 mol) and a crystal of iodine in dry ether (5 cm^3) was added 2-(3,4-dimethoxyphenyl)bromoethane (169, 9.26 g, 0.038 mol) in dry ether (15 cm^3). The magnesium failed to dissolve, even on stirring overnight.

(b) To magnesium turnings (0.1 g, 4.1 mmol), thoroughly dried at 60° in vacuo prior to use, and a small crystal of iodine in dry tetrahydrofuran (2 cm^3, freshly distilled from lithium aluminium hydride) was added 2-(3,4-dimethoxyphenyl)bromoethane (169, 1.0 g, 4.1 mmol) in dry tetrahydrofuran (10 cm^3). The mixture was heated under reflux for 3 hours. No reaction was seen to occur.

(c) To dried magnesium turnings (0.5 g, 0.02 mol) and a small crystal of iodine covered by dry ether (2 cm^3) was added a few drops of bromoethane. As soon as a vigorous reaction started the reaction vessel was cooled to arrest the reaction and the liquid was decanted off. 2-(3,4-Dimethoxyphenyl)bromoethane (169, 5 g, 0.02 mol) in dry ether (20 cm^3) was added. No reaction occurred even after heating

for 3 hours and stirring overnight at room temperature.

Attempted preparation of 3,4-dimethoxyphenethyllithium (174)

(a) To freshly cut lithium metal (0.14 g, 0.02 mol) in dry ether (20 cm^3) under nitrogen was added 2-(3,4-dimethoxyphenyl)bromoethane (169, 5 g, 0.02 mol) in dry ether (30 cm^3). The mixture was stirred overnight but the lithium failed to react.

(b) To a mixture of redistilled diisopropylamine (2.06 g, 2.85 cm^3, 0.02 mol) and dry tetrahydrofuran (10 cm^3) at 0^o was added 1.6 M n-butyllithium in hexane (12.75 cm^3, 0.02 mol). The pale yellow solution was maintained at 0^o for 0.5 hours and then was added hexamethylphosphoramide (3.65 g, 3.55 cm^3, 0.02 mol). The mixture was stirred at 0^o for a further 0.25 hours and then was added a solution of 2-(3,4-dimethoxyphenyl)bromoethane (169, 5 g, 0.02 mol) in dry tetrahydrofuran (20 cm^3). The mixture was stirred at 0^o for 0.5 hours and then added dropwise to a solution of 2-carbethoxyindole (165, 3.86 g, 0.02 mol) in dry tetrahydrofuran (20 cm^3). The reaction mixture was stirred for 1 hour at room temperature and then poured into 10% hydrochloric acid (100 cm^3) and extracted with ether (3 x 100 cm^3). The combined organic phases were washed with water (2 x 50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a white solid. Thin layer chromatographic analysis (silica/dichloromethane) showed there to be two components, 2-carbethoxyindole and 2-(3,4-dimethoxyphenyl)bromoethane.

Butan-2,3-dione monophenylhydrazone (177)

Ethyl 2-methylacetoacetate (3g, 2.9 cm^3, 0.021 mol) was added to a solution of potassium hydroxide (1.25 g) in water (47 cm^3), and then

stirred for 24 hours and acidified with 2N hydrochloric acid (12 cm^3).

Freshly distilled aniline (1.93 g, 1.9 cm^3, 0.021 mol) was added to 5N hydrochloric acid (15 cm^3) and cooled to 0^o, and then was added a solution of sodium nitrite (1.63 g) in water (5 cm^3).

The solution of 2-methylacetoacetic acid (175) was cooled to 0^o and to it was added the solution of benzenediazonium chloride. Excess sodium acetate (17 g) was added and the mixture stirred for 5 minutes. The red precipitate was collected by filtration, washed well with 2N sodium carbonate solution and water, and then recrystallised from petroleum ether as orange needles (2.1 g, 57%) m.p. 135^o.

$\bar{\nu}$ max (cm^{-1}) : 3260 (N-H), 1645 (C=O), 1595 (C=N)

λ max (nm (log ε)) : 208 (3.81), 238 (4.05), 300 (3.83), 345 (4.32)

δ (ppm, DMSO) : 1.97 (3H, s, $C\underline{H}_3$), 2.38 (3H, s, $COC\underline{H}_3$), 6.8 - 7.4 (5H, complex, aromatics), 9.87 (1H, s, $N\underline{H}$, removed by deuteration)

$\underline{m/e}$: 176 ($M^{+\cdot}$), 161 ($M-CH_3$), 133 ($M-COCH_3$), 106 (PhNHN), 99 (M-Ph), 92 (PhNH), 77 (Ph)

Metastable M^* at 100.5 (176 → 133)

Attempted preparation of 2-acetylindole (44)

(a) Butan-2,3-dione monophenylhydrazone (177, 1.0 g, 5.68 mmol) was dissolved in 3N ethanolic hydrochloric acid (5 cm^3) and heated under reflux for 1 hour. The reaction mixture was cooled and diluted with water (50 cm^3). The precipitate was collected by filtration, washed with water and recrystallised from methanol to return the starting material (0.98 g, 98%).

(b) Hydrazone (177, 1.0 g, 5.68 mmol) was heated under reflux

for 1 hour in glacial acetic acid (5 cm^3). Cooling and dilution with water returned the starting material unchanged.

(c) The hydrazone (177, 1.0 g, 5.68 mmol) was added to polyphosphoric acid (4 g) and warmed on a water bath. The temperature rose within a few seconds to 170°. The mixture was cooled, diluted with water (50 cm^3) and extracted with ether, but no organic material was recovered.

(d) The hydrazone (177, 0.2 g) was heated under reflux in diethylene glycol (2 cm^3) for 5 hours. The solution was cooled and diluted with water (10 cm^3). The precipitated starting material was collected and recrystallised from ethanol (0.18 g, 90%).

(e) The hydrazone (177, 1.0 g) was dissolved in 20% polyphosphoric ester in chloroform (25 cm^3) and heated under reflux for 0.5 hours. The solvent was removed under reduced pressure and the residue treated with water (100 cm^3) and extracted with ether (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the starting material (0.96 g, 96%).

Polyphosphoric ester

Phosphorus pentoxide (60 g) was added to chloroform (60 cm^3) and dry ether (120 cm^3) and heated under reflux for 3 hours. Excess phosphorus pentoxide was removed by filtration. The solvent was removed under reduced pressure to leave a colourless oil (71 g) which was dissolved in chloroform to form a 20% w/v solution.

1-(3,4-Dimethoxyphenyl)buten-3-one (179)

3,4-Dimethoxybenzaldehyde (178, 10 g, 0.06 mol) was dissolved in

Analar acetone (20 cm^3) and added to water (300 cm^3). 30% Sodium hydroxide solution (1.5 cm^3) was added and the reaction mixture stirred for 20 hours at room temperature. The bright yellow solid was collected by filtration and recrystallised from methanol (10.5 g, 85%) m.p. 81°.

$\bar{\nu}$ max (cm^{-1}) : 1670 (C=O)

λ max (nm (log ε)) : 207 (4.09), 226 (3.98), 245 (4.01), 342 (4.23)

δ (ppm, $CDCl_3$) : 2.39 (3H, s, $C\underline{H}_3$), 3.93 (6H, s, 2 x $OC\underline{H}_3$), 6.60 (1H, d, $C\underline{H}CO$, $\underline{J}$ = 16H_z), 6.88 (1H, d, $C_5\underline{H}$, $\underline{J}$ = 8H_z), 7.09 (1H, d, $C_2\underline{H}$, $\underline{J}$ = 2H_z), 7.12 (1H, dd, $C_6\underline{H}$, $\underline{J}_{56}$ = 8H_z, $\underline{J}_{26}$ = 2H_z), 7.48 (1H, d, $C\underline{H}$, $\underline{J}$ = 16H_z).

$\underline{m/e}$: 206 (M^+), 191 ($M-CH_3$), 163 ($M-COCH_3$), 151 ($ArCH_2$)

Metastable M^* at 177.1 (206 → 191) and 139.1 (191 → 163).

Attempted preparation of 1-(3,4-dimethoxyphenyl)-5-(2-nitrophenyl)penta-1,4-dienone

(a) To a stirred solution of sodium hydroxide (0.48 g, 0.012 mol) in water (5 cm^3) was added a solution of 1-(3,4-dimethoxyphenyl)buten-3-one (179, 2.0 g, 97 mmol) in ethanol (5 cm^3) followed by a solution of 2-nitrobenzaldehyde (1.47 g, 9.7 mmol) in ethanol (5 cm^3). The deep red solution was stirred for 3 days and then added to water (50 cm^3) and extracted with dichloromethane (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a black oil which could not be purified.

(b) A solution of sodium hydroxide (0.48 g, 0.012 mol) in water (5 cm^3) was cooled on ice and to it was added a solution of the ketone

(179, 2.0 g, 9.7 mmol) in ethanol (2.5 cm^3). A solution of 2-nitrobenzaldehyde (1.47 g, 9.7 mmol) was added dropwise at such a rate that the temperature did not exceed 25°. The mixture was stirred for 4 hours at room temperature, added to water (150 cm^3) and worked-up as above to give an intractable red oil.

(c) 2-Nitrobenzaldehyde (1.51 g, 0.01 mol) and the ketone (179, 2.06 g, 0.01 mol) were heated with piperidine (0.12 cm^3) at 130° for 2 hours. The mixture was cooled to 100° and glacial acetic acid (4 cm^3) added to take up the piperidine. The mixture was added to water (50 cm^3) and extracted with chloroform (3 x 20 cm^3). The combined organic phases were washed with water (20 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a solid which was shown to be a mixture of the two starting materials by thin layer chromatography and mass spectrometry.

4,5,6,7-Tetrahydroindole (181)

To liquid ammonia (200 cm^3) contained in a Dewar vessel was added a solution of indole (13, 4.68 g, 0.04 mol) in dry methanol (24 cm^3). Then lithium metal (1.12 g, 0.16 mol) was added portionwise and the mixture stirred overnight to allow the ammonia to evaporate. The residue was treated with water (100 cm^3) and extracted with ether (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residual brown oil (4.61 g) dissolved in ethyl acetate (100 cm^3) and hydrogenated (2 atm) overnight with 10% palladium on carbon (0.1 g) as catalyst. Filtration and removal of the solvent under reduced pressure followed by vacuum distillation gave the product (181) as a colourless oil (b.p. 96° at 0.4 mm Hg) which

crystallised on standing (4.17 g, 86%) m.p. 52° (lit.[15] m.p. 55°).

$\bar{\nu}$ max (cm^{-1}) : 3360 (N-H)

δ (ppm, $CDCl_3$) : 1.7 - 1.9 (4H, complex, 2 x $\underline{CH}_2$), 2.5 - 2.6 (4H, complex, 2 x $\underline{CH}_2$), 5.95 (1H, d, $C_3\underline{H}$, $\underline{J}$ = $3H_2$), 6.55 (1H, d, $C_2\underline{H}$, $\underline{J}$ = $3H_2$), 7.4 - 7.8 (1H, broad, $N\underline{H}$, removed by deuteration)

$\underline{m/e}$: 121 ($M^{+\cdot}$)

This compound was used immediately since it was found to decompose on standing.

2-(3,4-Dimethoxyphenylpropanoyl)-4,5,6,7-tetrahydroindole (184)

To dried magnesium turnings (4.86 g, 0.19 mol) and a crystal of iodine in dry ether (50 cm^3) was added bromoethane (19.71 g, 13.5 cm^3, 0.18 mol) in dry ether (100 cm^3). To this was added dropwise a solution of 4,5,6,7-tetrahydroindole (181, 20 g, 0.165 mol) in dry ether (150 cm^3). The mixture was heated under reflux for 0.5 hours and then added dropwise to a solution of methyl 3,4-dimethoxyphenylpropanoate (159, 37 g, 0.165 mol) in dry ether (400 cm^3). The reaction mixture was stirred at room temperature under nitrogen for 1 week and then poured into 2N hydrochloric acid (1 dm^3) and extracted with dichloromethane (3 x 400 cm^3). The combined organic phases were washed with water (250 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a red gum which was boiled with propan-2-ol (50 cm^3). On cooling the precipitate was collected by filtration and recrystallised from ethanol as fine white needles (9.08 g, 17.6%) m.p. 121°.

$\bar{\nu}$ max (cm^{-1}) : 3250 (N-H), 1610 (C=O)

λ max (nm (log ε)) : 207 (4.34), 226 (3.98), 265 (3.69), 322 (4.26)

δ (ppm, $CDCl_3$) : 1.6 - 1.9 (4H, complex, $C_5\underline{H}_2$,$C_6\underline{H}_2$), 2.4 - 2.7 (4H, complex, C_4, $\underline{H}_2$, $C_7\underline{H}_2$), 2.99 (4H, s, $C\underline{H}_2C\underline{H}_2$), 3.83 (6H, s, 2 x $OC\underline{H}_3$), 6.66 (1H, s, $C_3\underline{H}$), 6.76 (3H, complex, aromatics), 9.76 (1H, s, N$\underline{H}$, removed by deuteration)

$\underline{m/e}$: 313 ($M^{+\cdot}$), 151 ($ArCH_2$), 121 (tetrahydroindole)

2-(3,4-Dimethoxyphenylpropanoyl)indole (154)

2-(3,4-Dimethoxyphenylpropanoyl)-4,5,6,7-tetrahydroindole (184, 1 g, 3.2 mmol) and dichlorodicyanobenzoquinone (1.74 g, 7.7 mmol) were heated under reflux in dry toluene (5 cm^3) for 20 hours. The precipitated quinol was removed by filtration and washed with chloroform. The filtrate was evaporated under reduced pressure and the residual orange solid recrystallised from methanol as fine orange needles (0.47 g, 47.6%) m.p. 159°.

$\bar{\nu}$ max (cm^{-1}) : 3320 (N-H), 1650 (C=O)

λ max (nm (log ε)) : 216 (4.53), 227 (4.35), 312 (4.35)

δ (ppm, $CDCl_3$) : 3.0 - 3.3 (4H, 2t, $C\underline{H}_2C\underline{H}_2$, $\underline{J}$ = 6H_z), 3.82 (6H, s, 2 x $OC\underline{H}_3$), 6.74 (3H, complex, aromatics), 7.0 - 7.7 (5H, complex, indole aromatics), 9.52 (1H, broad, N$\underline{H}$, removed by deuteration)

δ (ppm, DMSO) : 29.69 (t, 2 x $\underline{C}H_2$), 55.48 (q, 2 x $O\underline{C}H_3$), 108.79 (d), 112.20 (d), 112.63 (d), 120.06 (d), 122.44 (d), 125.20 (d), 126.88 (s), 133.60 (s), 135.39 (s), 137.72 (s), 147.25 (s), 148.77 (s), 191.84 (s, C=O)

$\underline{m/e}$: 309 ($M^{+\cdot}$), 151 ($ArCH_2$), 117 (indole)

Found : C, 73.7; H, 6.2; N, 4.6.

$C_{19}H_{19}NO_3$ requires : C, 73.8; H, 6.15; N, 4.6%.

Anodic oxidation of 2-(3,4-dimethoxyphenylpropanoyl)indole (154)

(a) 2-(3,4-Dimethoxyphenylpropanoyl)indole (154, 1 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (150 cm^3) and electrolysed at an anode potential of + 1.1 - 1.2 volts until the current dropped to 10 mA and $3F.mol^{-1}$ of charge had been consumed. The anolyte was partially evaporated under reduced pressure and the residue treated with water (200 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a black solid which was chromatographed on silica eluting with ether. The starting material (154, 0.1 g, 10%) was obtained but the rest of the material was a tar.

(b) The substrate (154, 1 g) was oxidised as above at a potential of + 0.8 - 1.0 volts until $2F.mol^{-1}$ of charge had been consumed. Work-up gave a tarry residue and starting material (0.67g, 67%).

Palladium acetate oxidation of 3-(3,4-dimethoxyphenylpropanoyl)indole (74)

(a) 3-(3,4-Dimethoxypheylpropanoyl)indole (74, 0.62 g, 2 mmol) and palladium acetate (0.22 g, 1 mmol) were heated under reflux in glacial acetic acid (80 cm^3) under nitrogen for 20 hours. Evaporation of the solvent under reduced pressure followed by column chromatography on silica eluting with 50% ether in petroleum ether gave a yellow solid which could not be separated into its components.

$^m/_e$: 351, 309, 307

(b) The indole (74, 0.31 g, 1 mmol) and palladium acetate (0.22 g, 1 mmol) were heated under reflux in glacial acetic acid (60 cm^3) under nitrogen for 20 hours. The reaction was worked-up as above.

Preparative liquid chromatography on a pre-packed silica column eluting with 35% ethyl acetate in petroleum ether gave the substrate (0.15 g, 48%) but no further separation was achieved.

(c) The indole (74, 0.93 g, 3 mmol) and palladium acetate (1.34 g, 6 mmol) were heated under reflux in glacial acetic acid (200 cm^3) for 20 hours. Separation of the products again proved to be impossible.

(d) The indole (74, 1.55 g, 5 mmol), palladium acetate (0.56 g, 2.5 mmol) and copper acetate (5 g, 25 mmol) were heated under reflux in glacial acetic acid (300 cm^3) for 16 hours. The solvent was evaporated under reduced pressure and the residue added to water (500 cm^3) and extracted with chloroform (3 x 200 cm^3). The combined organic phases were washed with water (200 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure followed by chromatography on silica eluting with ether gave a solid which could not be separated.

$^m/_e$: 351, 309

(e) The indole (74, 1.55 g, 5 mmol), palladium acetate (0.11 g, 0.5 mmol) and copper acetate (0.1 g, 0.5 mmol) were heated under reflux for 18 hours in dry acetonitrile (500 cm^3). Oxygen was bubbled through the reaction. Work-up in the usual way gave starting material (0.79 g, 51%).

(f) The indole (74, 0.93 g, 3 mmol) and palladium acetate (0.67 g, 3 mmol) were heated under reflux in dry acetonitrile (100 cm^3) for 3 days. Thin layer chromatography showed that no reaction had occurred.

1-Methyl-3-(3,4-dimethoxyphenylpropanoyl)indole (186)

To a solution of potassium hydroxide (4.5 g) in dry dimethylsulph-

oxide (40 cm^3) under nitrogen was added 3-(3,4-dimethoxyphenylpropanoyl)indole (74, 3.09 g, 0.01 mol). The solution was stirred for 3 hours and then was added iodomethane (1.5 g, 0.7 cm^3, 0.011 mol). The mixture was stirred overnight at room temperature and then diluted with water (90 cm^3). The solid was collected by filtration, washed with water and recrystallised from methanol to give the product (186) as pale yellow crystals (2.12 g, 66%) m.p. 114°.

$\bar{\nu}$ max (cm^{-1}) : 1640 (C=O)

λ max (nm (log ε)) : 208 (4.51), 247 (4.13), 310 (4.06)

δ (ppm, DMSO) : 2.8 - 3.3 (4H, complex, 2 x $C\underline{H}_2$), 3.69 (3H, s, $OC\underline{H}_3$), 3.73 (3H, s, $OC\underline{H}_3$), 3.78 (3H, s, $NC\underline{H}_3$), 6.8 - 6.9 (3H, complex, aromatics), 7.2 - 7.5 (3H, complex, indole aromatics), 8.2 - 8.4 (2H, complex, indole aromatics)

$\underline{m/e}$: 323 ($M^{+\cdot}$), 151 ($ArCH_2$)

Palladium acetate oxidation of 1-methyl-3-(3,4-dimethoxyphenylpropanoyl)-indole (186)

The substrate (186, 0.97 g, 3 mmol) and palladium acetate (1.34 g, 6 mmol) were heated under reflux in glacial acetic acid (200 cm^3) for 16 hours. Work-up in the usual way returned the starting material (0.94 g, 97%).

3-(3,4-Dimethoxyphenylacetyl)indole (73)

3,4-Dimethoxyphenylacetic acid (19.6 g, 0.1 mol) was heated under reflux for 0.5 hours with redistilled thionyl chloride (30 cm^3) in dry toluene (100 cm^3). Removal of the solvent under reduced pressure gave a red oil which was used immediately.

To dried magnesium turnings (2.9 g, 0.12 mol) and a small crystal

of iodine in dry ether (30 cm^3) was added bromoethane (10.9 g, 7.46 cm^3, 0.1 mol) in dry ether (50 cm^3). Indole (13, 11.7 g, 0.1 mol) in dry ether (50 cm^3) was added dropwise followed by dichloromethane (10 cm^3).

The Grignard reagent was added dropwise to a solution of the acid chloride (142) in dry ether (100 cm^3) with cooling on ice. The mixture was stirred at room temperature for 3 days and then hydrolysed with 2N hydrochloric acid (400 cm^3) and extracted with chloroform (3 x 200 cm^3). The combined organic phases were washed with water (200 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure left a viscous red oil which was boiled with methanol (20 cm^3). On cooling the solid was collected by filtration and recrystallised from methanol as colourless needles (4.75 g, 16%) m.p. 181°.

$\bar{\nu}$ max (cm^{-1}) : 3170 (N-H), 1630 (C=O)

λ max (nm (log ε)) : 211 (4.31), 262 (4.04), 250 (3.81), 291 (3.87), 302 (3.90)

δ (ppm, DMSO) : 3.68 (3H, s, $OC\underline{H}_3$), 3.71 (3H, s, $OC\underline{H}_3$), 4.0H (2H, s, $C\underline{H}_2$), 6.8 - 8.2 (7H, complex, aromatics), 8.41 (1H, s, $C_2\underline{H}$), 11.76 (1H, broad s, $N\underline{H}$, removed by deuteration)

$\underline{m/e}$: 295 ($M^{+\cdot}$), 151 ($ArCH_2$), 144 ($M-ArCH_2$), 116 (indole)

Metastables M^* at 93.4 (144 → 116) and 703 (295 → 144)

Palladium acetate oxidation of 3-(3,4-dimethoxyphenylacetyl)indole (73)

The indole (73, 1.47 g, 5 mmol) and palladium acetate (2.25 g, 0.01 mol) were heated under reflux in glacial acetic acid (400 cm^3) for 18 hours. Work-up in the usual way returned the starting material unchanged.

3,4-Dimethoxybenzoyl chloride (188)

3,4-Dimethoxybenzoic acid (18.2 g, 0.1 mol) and redistilled thionyl chloride (40 cm^3) were heated under reflux in dry toluene (100 cm^3) for 1.5 hours. Removal of the solvent under reduced pressure gave a white solid which was used immediately (20 g, 97%).

3-(3,4-Dimethoxybenzoyl)indole (189)

To dried magnesium turnings (2.9 g, 0.12 mol) and a crystal of iodine in dry ether (10 cm^3) was added bromoethane (10.9 g, 7.5 cm^3, 0.1 mol) in dry ether (20 cm^3). Indole (13, 11.7 g, 0.1 mol) in dry ether (40 cm^3) was added followed by dry dichloromethane (10 cm^3).

3,4-Dimethoxybenzoyl chloride (188, 20 g, 0.1 mol) was dissolved in dry ether (100 cm^3) and to it was added the solution of the Grignard reagent (41) prepared above. The mixture was stirred for 3 days at room temperature and then hydrolysed with 2N hydrochloric acid (400 cm^3) and extracted with chloroform (3 x 500 cm^3). The combined organic phases were washed with water (500 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a pink gum which was boiled with methanol (50 cm^3). On cooling the pale yellow solid was collected by filtration and recrystallised from methanol as colourless needles (13.15 g, 47%) m.p. 199°.

$\bar{\nu}$ max (cm^{-1}) : 3160 (N-H), 1610 (C=O)

λ max (nm (log ε)) : 214 (4.63, 257 (3.87), 265 (3.87), 272 (3.89), 325 (3.97)

δ (ppm, DMSO) : 3.82 (6H, s, 2 x $OC\underline{H}_3$), 7.04 (1H, d, $C_5\underline{H}$, $\underline{J}$ = $8H_2$), 7.1 - 7.3 (2H, complex, $C_5\underline{H}$, $C_6\underline{H}$), 7.4 - 7.6 (2H, complex, $C_6\underline{H}$, $C_7\underline{H}$), 7.41 (1H, s,

$C_2\underline{H}$), 8.01 (1H, d, $C_2,\underline{H}$, $\underline{J}$ = $2H_3$), 8.2 - 8.3 (1H, complex, $C_4\underline{H}$)

$\underline{m/e}$: 281 ($M^{+\cdot}$), 266 ($M-CH_3$), 165 (ArCO), 144 (M-Ar), 116 (indole)

Palladium acetate oxidation of 3-(3,4-dimethoxybenzoyl)indole (189)

(a) The indole (189, 2.81 g, 0.01 mol) and palladium acetate (4.48 g, 0.02 mol) were heated under reflux for 24 hours in glacial acetic acid (500 cm^3). Removal of the solvent under reduced pressure gave a tarry solid which was chromatographed on silica eluting with ether to give a trace amount of a yellow solid.

$\underline{m/e}$: 279

(b) The above reaction was repeated with acetonitrile (250 cm^3) as solvent. The substrate failed to react at all.

1-Methyl-3-(3,4-dimethoxybenzoyl)indole (190)

Potassium hydroxide (2.3 g) was dissolved in dry dimethylsulphoxide (40 cm^3) under nitrogen. 3-(3,4-Dimethoxybenzoyl)indole (189, 2.81 g, 0.01 mol) was added and the solution stirred for 3 hours. Iodomethane (1.5 g, 0.7 cm^3, 0.011 mol) was added and the mixture stirred for 20 hours at room temperature and then diluted with water (100 cm^3). The precipitate was collected by filtration, washed with water and recrystallised from methanol as white needles (2.49 g, 84%) m.p. 131°.

$\bar{\nu}$ max (cm^{-1}) : 1615 (C=O)

λ max (nm (log ε)) : 216 (4.58), 264 (4.22), 330 (4.24)

δ (ppm, DMSO) : 3.85 (6H, s, 2 x $OC\underline{H}_3$), 3.86 (3H, s, $NC\underline{H}_3$), 7.02 (1H, d, $C_2,\underline{H}$, $\underline{J}$ = $7H_3$), 7.2 - 7.5 (5H, complex, aromatics), 7.96 (1H, s, $C_2\underline{H}$),

8.2 - 8.3 (1H, complex, $C_4\underline{H}$)

$\underline{m/e}$: 295 ($M^{+\cdot}$), 158 (M-Ar), 130 (M-Ar-CO)

4-Methyl-8,9-dimethoxy-4,6-dihydronaphtho[3,2,1-c,d]indol-6-one (191)

1-Methyl-3-(3,4-dimethoxybenzoyl)indole (190, 1.47 g, 5 mmol) and palladium acetate (1.12 g, 5 mmol) were heated under reflux in glacial acetic acid (150 cm^3) for 18 hours. The solvent was removed under reduced pressure and the residue chromatographed on silica eluting with ether. The initial fractions were all mixtures, but evaporation of the final fractions under reduced pressure and recrystallisation from ethanol gave (191) as a red solid (0.03 g, 3.2%) m.p. 211°.

$\bar{\nu}$ max (cm^{-1}) : 1680 (C=O)

λ max (nm (log ε)) : 208 (4.24), 229 (4.08), 239 (4.08), 246 (4.07), 255 (4.08), 286 (4.53)

δ (ppm, CF_3COOD) : 3.32 (3H, s, $NC\underline{H}_3$), 3.77 (6H, s, 2 x $OC\underline{H}_3$), 6.38 (1H, s), 6.52 (1H, s), 6.7 - 7.4 (4H, complex, aromatics)

$\underline{m/e}$: 293 ($M^{+\cdot}$), 278 ($M-CH_3$), 250 ($M-CH_3-CO$)

Metastable M^* at 263.8 (293 → 278)

Found : C, 77.75; H, 5.0; N, 4.8.

$C_{18}H_{15}NO_3$ requires : C, 77.8; H, 5.1 ; N, 4.8%

3-Benzoylindole (192)

To dried magnesium turnings (2.9 g, 0.12 mol) and a crystal of iodine in dry ether (10 cm^3) was added bromoethane (10.9 g, 7.5 cm^3, 0.1 mol) in dry ether (20 cm^3) followed by a solution of indole (13, 11.7 g, 0.1 mol) in dry ether (40 cm^3). The mixture was stirred for 0.25 hours and then homogenised by the addition of dry dichloromethane

($10\ cm^3$). The Grignard reagent (41) was then added dropwise to benzoyl chloride (14.05 g, $11.6\ cm^3$, 0.1 mol) in dry ether ($100\ cm^3$). The reaction mixture was stirred at room temperature for 6 days and then hydrolysed with 2N hydrochloric acid ($400\ cm^3$) and extracted with chloroform ($3 \times 500\ cm^3$). The combined organic phases were washed with water ($500\ cm^3$) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a pale yellow solid which was recrystallised twice from methanol as white crystals (5.72 g, 26%) m.p. 214^o.

$\bar{\nu}$ max (cm^{-1}) : 3130 (N-H), 1605 (C=O)

λ max (nm (log ε)) : 215 (4.35), 251 (4.10), 267 (3.91), 319 (3.93)

δ (ppm, DMSO) : 7.3 - 7.9 (8H, complex, aromatics), 7.97 (1H, s, $C_2\underline{H}$), 8.37 (1H, complex, $C_4\underline{H}$), 12.05 (1H, broad s, $N\underline{H}$, removed be deuteration)

$\underline{m/e}$: 221 ($M^{\cdot+}$), 144 (M-Ph), 116 (indole), 105 (PhCO), 77 (Ph)

Metastables M^* at 93.8 (221 → 144) and 56.5 (105 → 77)

4,6-Dihydronaphtho[3,2,1-c,d,]indol-6-one (193)

3-Benzoylindole (192, 2.21g, 0.01 mol) and palladium acetate (4.48 g, 0.02 mol) were heated under reflux in glacial acetic acid ($500\ cm^3$) for 20 hours. The solvent was removed under reduced pressure to give a red solid which was chromatographed on silica eluting with dichloromethane.

Evaporation of the initial fractions under reduced pressure and recrystallisation from ether gave 1,3-dibenzoylindole (194) as fine yellow needles (0.02 g, 1.2%).

$\bar{\nu}$ max (cm^{-1}) : 1700 (NC=O), 1640 (C=O)

λ max (nm (log ε)) : 209 (4.64), 240 (4.58), 319 (4.17)

δ (ppm, DMSO) : 7.5 - 8.1 (12H, complex, aromatics), 7.84 (1H, s, $C_2\underline{H}$), 8.3 - 8.5 (2H, complex, $C_4\underline{H}$, $C_7\underline{H}$)

$\underline{m/e}$: 325 ($M^{+\cdot}$), 105 (PhCO)

Found : C, 81.2; H, 4.65; N, 4.4.

$C_{22}H_{15}NO_2$ requires : C, 81.2; H, 4.6; N, 4.3%.

Evaporation of the later fractions under reduced pressure and recrystallisation from ethanol gave the title compound (193) as bright red rods (0.74 g, 34%) m.p. >250°.

$\bar{\nu}$ max (cm^{-1}) : 3150 (N-H), 1660 (C=O)

λ max (nm (log ε)) : 209 (4.21), 223 (4.29), 229 (4.28), 237 (4.23), 246 (4.19), 262 (4.53), 281 (4.62), 308 (3.99), 320 (3.98)

δ (ppm, DMSO) : 7.1 - 7.7 (8H, complex aromatics and $N\underline{H}$), 7.37 (1H, s, $C_2\underline{H}$)

δ (ppm, DMSO) : 113.55 (d), 114.21 (s), 118.97 (d), 119.35 (d), 122.27 (d), 122.49 (s), 122.81 (d), 122.98 (d), 129.58 (d), 131.40 (d), 134.68 (s), 140.47 (s), 141.77 (s), 158.57 (s), 184.41 (s, C=O).

$\underline{m/e}$: 219 ($M^{+\cdot}$), 190 (M-HCHO)

Found : C, 82.1; H, 4.15; N, 6.4.

$C_{15}H_9NO$ requires : C, 82.2; H, 4.1; N, 6.4%.

2-(3,4-Dimethoxyphenylacetyl)-4,5,6,7-tetrahydroindole

To dried magnesium turnings (6.08 g, 0.25 mol) and a crystal of iodine in dry ether (50 cm^3) was added bromoethane (24.6 g, 16.9 cm^3, 0.23 mol) in dry ether (100 cm^3) followed by a solution of 4,5,6,7-tetrahydroindole (181, 25 g, 0.21 mol) in dry ether (150 cm^3). The

mixture was stirred at room temperature for 4 days and then hydrolysed with 2N hydrochloric acid (1 dm^3) and extracted with dichloromethane (3 x 400 cm^3). The combined organic phases were washed with water (250 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a pale yellow oil which was boiled with propan-2-ol (25 cm^3). On cooling the solid was collected by filtration and recrystallised from methanol as colourless needles (11.57 g, 16.8%) m.p. 168°.

$\bar{\nu}$ max (cm^{-1}) : 3250 (N-H), 1620 (C=O)

λ max (nm (log ε)) : 206 (4.13), 224 (3.88), 258 (3.44), 319 (4.17)

δ (ppm, DMSO) : 1.7 - 2.5 (8H, complex, 4 x $C\underline{H}_2$), 3.70 (6H, s, 2 x $OC\underline{H}_3$), 3.83 (2H, s, $C\underline{H}_2CO$), 6.7 - 6.9 (4H, complex, aromatics), 11.11 (1H, broad s, $N\underline{H}$, removed by deuteration)

$\underline{m/e}$: 299 ($M^{+\cdot}$), 151 ($ArCH_2$), 148 ($M-ArCH_2$)

2-(3,4-Dimethoxyphenylacetyl)indole (155)

2-(3,4-Dimethoxyphenylacetyl)-4,5,6,7-tetrahydroindole (3 g, 0.01 mol) and dichlorodicyanobenzoquinone (5.5 g, 0.024 mol) were heated under reflux in dry toluene (25 cm^3) for 6 hours. The precipitated quinol was removed by filtration and washed with chloroform. Removal of the solvent under reduced pressure gave a tarry solid which was chromatographed on silica eluting with 30% ethyl acetate in petroleum ether. Removal of the solvent from the eluate under reduced pressure followed by recrystallisation from absolute ethanol gave the product (155) as pale orange needles (0.82 g, 28%) m.p. 176°.

$\bar{\nu}$ max (cm^{-1}) : 3340 (N-H), 1650 (C=O)

λ max (nm (log ε)) : 205 (4.57), 229 (4.30), 314 (4.28)

δ (ppm, DMSO) : 3.68 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 4.15 (2H, s, CH_2), 6.8 - 7.7 (7H, complex, aromatics), 11.51 (1H, broad s, NH, removed by deuteration)

m/e : 295 ($M^{+\cdot}$), 151 ($ArCH_2$), 144 ($M-ArCH_2$), 116 (indole)

Palladium acetate oxidation of 2-(3,4-dimethoxyphenylacetyl)indole (155)

The indole (155, 0.15 g, 0.5 mmol) and palladium acetate (0.22 g, 1 mmol) were heated under reflux in glacial acetic acid (20 cm^3) for 17 hours. Removal of the solvent under reduced pressure gave an intractable black tar.

Thallium trifluoroacetate oxidation of 3-(3,4-dimethoxyphenylpropanoyl)-indole (74)

(a) The indole (74, 0.62 g, 2 mmol) and thallium trifluoroacetate (1.19 g, 2.2 mmol) were stirred under nitrogen at room temperature in dry dichloromethane (200 cm^3) for 20 hours. Thin layer chromatography (silica/ether) showed that no reaction had occurred.

(b) Thallium trifluoroacetate (1.02 g, 1.9 mmol) was suspended in dry dichloromethane (100 cm^3) at -78^o under nitrogen in the absence of light. The indole (74, 0.53 g, 1.7 mmol) was added and the mixture stirred at -78^o for 1 hour and then at room temperature for 20 hours. Thin layer chromatography showed that no reaction had occurred.

(c) The indole (74, 0.62 g, 2 mmol) and thallium trifluoroacetate (1.19 g, 2.2 mmol) were stirred at room temperature in trifluoroacetic acid (200 cm^3) under nitrogen in the absence of light for 3 days. The

solvent was removed under reduced pressure and the residue dissolved in chloroform and then filtered through silica to remove thallium containing components. Evaporation of the filtrate under reduced pressure gave a dark red intractable tar.

Anodic oxidation of 1-methyl-3-(3,4-dimethoxyphenylpropanoyl)indole (186)

The indole (186, 1 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (200 cm^3) and electrolysed at a potential of + 0.9 - 1.2 volts until the current dropped to below 10 mA. The solvent was evaporated under reduced pressure and the residue treated with water (300 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a red solid which was chromatographed on silica eluting with ether. The red colour disappeared and the only component isolated was the starting material (0.6 g, 60%).

3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (201)

3,4-Dimethoxybenzaldehyde (150, 33.2 g, 0.2 mol) was dissolved in ethanol (200 cm^3) at room temperature. Aminoacetaldehyde dimethyl-acetal (81, 21 g, 21.8 cm^3, 0.2 mol) was added and the mixture stirred for 1 hour. The Schiff base (200) was reduced by the portionwise addition of sodium borohydride (16 g). The mixture was then stirred for 3 days at room temperature. The solvent was removed under reduced pressure and the residue was treated with water (400 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an oil which was

vacuum distilled. After forerunning aminoacetal (81) the product distilled as a colourless oil (38.7 g, 76%) b.p. 143° at 5 mm Hg.

$\bar{\nu}$ max (cm^{-1}) : 3310 (N-H)

λ max (nm (log ε)) : 213 (3.86), 234 (3.84), 283 (3.40)

δ (ppm, $CDCl_3$) : 1.95 (1H, broad,s, NH, removed by deuteration)
2.70 (2H, d, CH_2CH, J = 6Hz), 3.32 (6H, s, 2 x OCH_3, acetal), 3.70 (2H, s, CH_2), 3.82 (6H, s, 2 x OCH_3), 4.50 (1H, t, CH, J = 6Hz), 6.80 (3H, complex, aromatics)

m/e : 255 (M^+), 223 (M-CH_3OH), 180 (M-$CH(OCH_3)_2$), 151 ($ArCH_2$)

4-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (202)

(a) 3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (201, 25 g, 0.1 mol) was dissolved in 6N ethanolic hydrochloric acid (500 cm^3) and stirred for 20 hours at room temperature. The mixture was basefied with 30% sodium hydroxide solution and extracted with chloroform (3 x 200 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an intractable orange gum.

(b) The acetal (201, 25 g, 0.1 mol) was dissolved in 6N hydrochloric acid (500 cm^3) with cooling on ice, and then stirred for 20 hours at room temperature. The mixture was basefied by the addition of 20% sodium hydroxide solution, with cooling, at such a rate that the temperature did not exceed 20°. The solution was extracted with chloroform (3 x 200 cm^3) and the combined organic phases washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Partial removal of the solvent under reduced pressure at 25° gave a white solid which was collected by filtration (0.78 g, 3.7%) m.p. 192°.

$\bar{\nu}$ max (cm^{-1}) : 3320 (N-H)

λ max (nm (log ε)) : 209 (4.48), 235 (3.96), 286 (3.62), 291 (3.57)

δ (ppm, CD_3OD) : 3.42 (2H, d, $C\underline{H}_2CH$, $\underline{J}$ = $7H_z$), 3.80 (6H, s, 2 x $OC\underline{H}_3$), 4.24 (2H, s, $C\underline{H}_2$), 4.80 (1H, t, $C\underline{H}$, $\underline{J}$ = $7H_z$), 6.80 (1H, s, aromatic), 7.02 (1H, s, aromatic)

$\underline{m/e}$: 209 ($M^{+\cdot}$), 151 ($ArCH_2$)

sulphonyl

N-4-Methylphenyl-N-3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (205)

3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (201, 5.1 g, 0.02 mol) was dissolved in dry pyridine (15 cm^3) and to it was added a solution of toluene-4-sulphonyl chloride (4.2 g, 0.022 mol) in dry pyridine (15 cm^3). The mixture was stirred at room temperature for 3 days and then added to water (100 cm^3) and extracted with ether (3 x 50 cm^3). The combined organic phases were washed with 0.5N hydrochloric acid (2 x 50 cm^3) and water (2 x 50 cm^3) and then dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil (8.1 g, 98%).

$\bar{\nu}$ max (cm^{-1}) : 1140 (s=O)

δ (ppm, $CDCl_3$) : 2.40 (3H, s, $C\underline{H}_3$), 3.18 (2H, d, $C\underline{H}_2CH$, $\underline{J}$ = $6H_z$), 3.23 (6H, s, 2 x $OC\underline{H}_3$, acetal), 3.71 (3H, s, $OC\underline{H}_3$), 381 (3H, s, $OC\underline{H}_3$), 4.33 (1H, t, $C\underline{H}$, $\underline{J}$ = $6H_z$), 4.37 (2H, s, $C\underline{H}_2$), 6.70 (3H, complex, aromatics), 7.30 (2H, d, aromatics, tosyl, $\underline{J}$ = $10H_z$), 7.73 (2H, d, aromatics, tosyl, $\underline{J}$ = $10H_z$)

$\underline{m/e}$: 409 ($M^{+\cdot}$), 254 (M-Ts), 151 ($ArCH_2$)

6,7-Dimethoxyisoquinoline (204)

(a) N-4-Methylphenylsulphonyl-N-3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (205, 2 g, 5 mmol) was dissolved in 1,4-dioxan (48 cm^3) in the absence of light under nitrogen. 6N Hydrochloric acid (4 cm^3) was added and the mixture heated under reflux for 20 hours. The mixture was poured into water (100 cm^3) and washed with ether (3 x 50 cm^3). The aqueous phase was basefied with 2N ammonium hydroxide solution (20 cm^3) and extracted with chloroform (3 x 50 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil (0.82 g, 86%).

$\bar{\nu}$ max (cm^{-1}) : 1620 (C=N)

δ (ppm, $CDCl_3$) : 4.02 (6H, s, 2 x $OC\underline{H}_3$), 7.09 (1H, s, $C_8\underline{H}$), 7.22 (1H, s, $C_5\underline{H}$), 7.94 (1H, d, $C_4\underline{H}$, $\underline{J}$ = $5H_2$), 8.43 (1H, d, $C_3\underline{H}$, $\underline{J}$ = $5H_2$), 9.07 (1H, s, $C_1\underline{H}$)

$\underline{m/e}$: 189 ($M^{+\cdot}$), 174 ($M-CH_3$)

The ethereal washings from this reaction were dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil which was subjected to column chromatography on silica eluting with dichloromethane. Evaporation of the eluate under reduced pressure gave a solid which was recrystallised from petroleum ether as colourless cubes (208) m.p. 74°.

$\bar{\nu}$ max (cm^{-1}) : 1135 (S=O)

λ max (nm (log ε)) : 209 (4.33), 239 (4.24)

δ (ppm, $CDCl_3$) : 2.36 (3H, s, $C\underline{H}_3$), 2.40 (3H, s, $C\underline{H}_3$), 7.0 - 7.4 (6H, complex aromatics), 7.48 (2H, d, aromatics, $\underline{J}$ = $8H_2$)

m/e : 278 ($M^{+\cdot}$), 155 ($ArSO_2$), 139 (ArSO), 123 (ArS), 91 (Ar).

(b) 3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (201, 16.75 g, 0.066 mol) was added dropwise to chlorosulphonic acid (45 cm^3) at -15° and stirred for 3 days at room temperature. The mixture was added cautiously to ice (200 g) and washed with ether (2 x 50 cm^3). The aqueous phase was basefied with sodium carbonate and extracted with ethyl acetate (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil (5.96 g, 48%).

2-Methyl-6,7-dimethoxyisoquinolinium iodide (199)

6,7-Dimethoxyisoquinoline (204, 0.57 g, 3 mmol) was dissolved in acetone (20 cm^3) and treated with iodomethane (8 cm^3). The solid was collected by filtration and recrystallised from ethanol as pale green needles (0.71 g, 72%) m.p. 225°.

$\bar{\nu}$ max (cm^{-1}) : 1610 (C=N)

λ max (nm (log ε)) : 204 (4.20), 223 (4.40), 257 (4.65), 320 (3.92)

δ (ppm, DMSO) : 4.01 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 4.41 (3H, s, NCH_3), 7.79 (2H, s, C_5H, C_8H), 8.31 (1H, d, C_4H, $J = 7Hz$), 8.55 (1H, d, C_3H, $J = 7Hz$), 9.57 (1H, s, C_1H)

m/e : 203 (M-HI), 189 ($M-CH_3I$), 142 (CH_3I), 127 (I).

2-Methyl-4-(3,4-dimethoxyphenylacetyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (197)

2-Methyl-6,7-dimethoxyisoquinolinium iodide (199, 3.31 g, 0.01 mol) was thoroughly dried at 90° in vacuo and then added portionwise to a

slurry of lithium aluminium hydride (1.2 g) in dry ether (150 cm^3) under nitrogen and stirred for 2 hours. Excess reductant was decomposed by the cautious addition of 30% potassium sodium tartrate solution. The mixture was filtered rapidly and dried over anhydrous sodium sulphate under nitrogen. To the stirred solution under nitrogen was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (2.06 g, 0.01 mol) in dry dichloromethane (20 cm^3) followed by a solution of 3,4-dimethoxyphenylacetic acid (70, 2.95 g, 0.015 mol) in dry dichloromethane (20 cm^3). The mixture was stirred under nitrogen at room temperature for 20 hours. The precipitate was collected by filtration and then added to dichloromethane (50 cm^3). The insoluble N,N'-dicyclohexylurea (1.6 g, 71%) was removed by filtration. The filtrate was washed with saturated sodium bicarbonate solution (3 x 25 cm^3) and water (25 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a solid which was recrystallised from methanol as pale green needles (0.99 g, 26%) m.p. 168°.

$\bar{\nu}$ max (cm^{-1}) : 1590 (C=O)

λ max (nm (log ε)) : 207 (4.53), 229 (4.34), 291 (4.16), 359 (3.87)

δ (ppm, $CDCl_3$) : 3.08 (3H, s, $NC\underline{H}_3$), 3.80 (2H, s, $C\underline{H}_2CO$), 3.86 (3H, s, $OC\underline{H}_3$), 3.89 (6H, s, 2 x $OC\underline{H}_3$), 3.92 (3H, s, $OC\underline{H}_3$), 4.49 (2H, s, $C\underline{H}_2N$), 6.44 (1H, s, $C_3\underline{H}$), 6.85 (3H, complex, aromatics), 7.47 (1H, s, $C_8\underline{H}$), 8.52 (1H, s, $C_5\underline{H}$)

(ppm, DMSO) : 42.53 (q, $NC\underline{H}_3$), 43.34 (t), 51.25 (t), 55.37 (q, 2 x $OC\underline{H}_3$), 55.53 (q, 2 x $OC\underline{H}_3$), 104.45 (S), 108.89 (d), 109.32 (d), 11.98 (S), 113.39 (S), 117.99 (d), 121.02 (d), 123.63 (d), 130.56 (S),

146.49 (S), 147.30 (S), 148.55 (S), 151.80 (d),

191.18 (S, C=O)

m/e : 383 ($M^{+\cdot}$), 368 (M-CH_3), 246 (M-Ar), 232 (M-$ArCH_2$), 151 ($ArCH_2$)

Found : C, 69.05; H, 6.55; N, 3.55.

$C_{22}H_{25}NO_5$ requires : C, 68.9; H, 6.5; N, 3.65%.

Anodic oxidation of 2-methyl-4-(3,4-dimethoxyphenylacetyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (197)

(a) The substrate (197, 0.5 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (100 cm^3) and electrolysed at a potential of + 1.2 volts until the current dropped to 10 mA. The anolyte was partially evaporated under reduced pressure and the residue treated with water (300 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a black tar.

(b) The substrate (197, 0.5 g) was electrolysed as described above, but at a potential of + 0.8 volts. Work-up again gave an intractable black tar.

Attempted preparation of 2-methyl-4-(3,4-dimethoxyphenylpropanoyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (198)

(a) 2-Methyl-6,7-dimethoxyisoquinolinium iodide (199, 3.3 g, 0.01 mol) was thoroughly dried at 90° in vacuo and then added to a slurry of lithium aluminium hydride (1.2 g) in dry ether (150 cm^3) under nitrogen and stirred for 2 hours. Excess reductant was decomposed by the cautious addition of 30% potassium sodium tartrate solution. The mixture was filtered rapidly and dried over anhydrous sodium sulphate under nitrogen. Then was added a solution of N,N'-dicyclohexylcarbo-

diimide (2.06 g, 0.01 mol) in dry dichloromethane (20 cm^3) followed by a solution of 3,4-dimethoxyphenylpropanoic acid (153, 3.14 g, 0.015 mol) in dry dichloromethane (20 cm^3). The mixture was stirred under nitrogen at room temperature for 20 hours. The precipitated N,N'-dicyclohexylurea was removed by filtration and washed with chloroform. The filtrate was washed with saturated sodium bicarbonate solution (3 x 75 cm^3) and water (75 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an oil which crystallised on standing. The solid was collected by filtration and then recrystallised from absolute ethanol to give N,N'-dicyclohexyl-N-3,4-dimethoxyphenylpropanoylurea (211) as pale green crystals (0.92 g, 22%) m.p. 141°.

$\bar{\nu}$ max (cm^{-1}) : 3270 (N-H), 1695 (C=O), 1650 (C=O)

λ max (nm (log ε)) : 207 (4.43), 225 (4.05), 282 (3.66)

δ (ppm, $CDCl_3$) : 1.0 - 2.0 (22H, complex, 2 x $C_6\underline{H}_{11}$), 2.6 - 3.0 (4H, 2 x t, $C\underline{H}_2C\underline{H}_2$, $\underline{J}$ = 7H_z), 3.7 (1H, broad, N$\underline{H}$), 3.86 (6H, s, 2 x O$C\underline{H}_3$), 6.7 - 6.8 (3H, complex, aromatics)

$\underline{m/e}$: 416 ($M^{+\cdot}$), 334 (M-C_6H_{10}), 291 (M-$C_6H_{11}NCO$), 151 ($ArCH_2$)

Metastables M^* at 268.2 (416 → 334) and 203.6 (416 → 291)

(b) The 1,2-dihydroisoquinoline (209) was prepared as described above. The solution was stirred under nitrogen and to it was added a mixture of 3,4-dimethoxyphenylpropanoic acid (153, 2.10 g, 0.01 mol) and 1-hydroxybenzotriazole hydrate (1.53 g, 0.01 mol) in dry dioxan (40 cm^3). A solution of N,N'-dicyclohexylcarbodiimide (2.06 g, 0.01 mol) in dry dichloromethane (20 cm^3) was then added dropwise and the mixture stirred at room temperature for 20 hours. The precipitated N,N'-dicyclohexylurea was removed by filtration and washed with chloroform. The

filtrate was washed with saturated sodium bicarbonate solution (3 x 50 cm^3) and water (2 x 50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown gum which was triturated with ethanol, but no crystallisation occurred. The gum was dissolved in dichloromethane (200 cm^3) and extracted with 2N hydrochloric acid (3 x 50 cm^3).

The organic phase was dried over anhydrous sodium sulphate and evaporated under reduced pressure to leave a brown oil. The oil was purified by column chromatography on silica eluting with ether. Evaporation of the eluate under reduced pressure gave ethyl 3,4-dimethoxyphenylpropanoate (216) as a colourless oil.

$\bar{\nu}$ max (cm^{-1}) : 1730 (C=O)

δ (ppm, $CDCl_3$) : 1.20 (3H, t, $CH_2\underline{CH}_3$, $\underline{J}$ = $7H_{\underline{J}}$), 2.60 (2H, t, $\underline{CH}_2CH_2$, $\underline{J}$ = $6H_{\underline{J}}$), 2.84 (2H, t, $CH_2\underline{CH}_2$, J = $6H_{\underline{J}}$), 3.84 (6H, s, 2 x $O\underline{CH}_3$), 4.08 (2H, q, $\underline{CH}_2CH_3$, J = $7H_{\underline{J}}$), 6.7 - 6.8 (3H, complex, aromatics)

$\underline{m/e}$: 238 ($M^{\cdot+}$), 164 ($ArCHCH_2$), 151 ($ArCH_2$)

The acidic phases were basefied with 2N ammonium hydroxide solution (250 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil which consisted of 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (210) and intractable polymeric material.

$\underline{m/e}$: 207/206

(c) The 1,2-dihydroisoquinoline (209, 0.01 mol) was prepared as above and the solution stirred at 0^o under nitrogen with triethylamine (1.51 g, 2.1 cm^3, 0.015 mol). A solution of 3,4-dimethoxyphenylpropanoyl chloride (149, 3.4 g, 0.015 mol) in ether (50 cm^3) was added

dropwise and the mixture stirred for 3 hours at 0° and then for 20 hours at room temperature. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate washed with water (3 x 50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an intractable brown gum.

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl isoquinolinium iodide (219)

3,4-Dimethoxybenzylaminoacetaldehyde dimethylacetal (201, 12.75 g, 0.05 mol) was dissolved in concentrated hydrochloric acid (125 cm^3) and then cooled to room temperature. A solution of 3,4-dimethoxybenzaldehyde (150, 16.6 g, 0.1 mol) in ethanol (125 cm^3) was added and the mixture heated under reflux for 0.5 hours and then cooled and diluted with water (250 cm^3). Excess aldehyde was removed by washing with ether (3 x 100 cm^3). The solution was basefied with concentrated ammonia and then boiled for 0.5 hours. The cooled mixture was extracted with dichloromethane (3 x 200 cm^3). The combined organic phases were washed with water (200 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a brown oil which was dissolved in acetone (60 cm^3) and treated with iodomethane (30 cm^3). The solid was collected by filtration and recrystallised from methanol as yellow needles (7.53 g, 31%) m.p. 231°.

$\bar{\nu}$ max (cm^{-1}) : 1635 (C=N)

λ (nm (log ε)) : 210 (4.56), 259 (4.54), 290 (3.15), 322 (3.63)

δ (ppm, DMSO) : 3.68 (3H, s, $OC\underline{H}_3$), 3.72 (3H, s, $OC\underline{H}_3$), 3.96 (3H, s, $OC\underline{H}_3$), 4.01 (3H, s, $OC\underline{H}_3$), 4.39 (3H, s, $NC\underline{H}_3$), 4.45 (2H, s, $C\underline{H}_2$), 6.8 - 7.1 (3H, complex aromatics), 7.61 (1H, s, $C_8\underline{H}$), 7.77 (1H, s, $C_5\underline{H}$), 8.49 (1H, s, $C_3\underline{H}$), 9.48 (1H, s, $C_1\underline{H}$)

m/e : 339 ($M-CH_3I$), 151 ($ArCH_2$), 142 (CH_3I), 127 (I)

2-Methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (220)

A suspension of the methiodide salt (219, 4.8 g, 0.01 mol) in ethanol (200 cm^3) was treated with sodium borohydride (8 g) and stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue dissolved in 2N hydrochloric acid (200 cm^3) to hydrolyse N-boranes, and then basefied with 2N sodium hydroxide solution (220 cm^3) and extracted with dichloromethane (3 x 200 cm^3). The combined organic phases were washed with water and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a yellow oil which was purified by column chromatography on basic alumina, eluting with ether to give the product as a white solid (2.57 g, 72%) m.p. 96°.

$\bar{\nu}$ max (cm^{-1}) : 1130 (aromatic ether)

λ max (nm (log ε)) : 213 (4.44), 233 (4.17), 286 (3.68), 289 (3.66)

δ (ppm, DMSO) : 2.1 - 3.6 (7H, complex, aliphatics), 2.28 (3H, s, NCH_3), 3.68 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 6.6 - 6.9 (5H, complex, aromatics)

m/e : 357 ($M^{\cdot+}$), 342 ($M-CH_3$), 219 (M-Ar), 151 ($ArCH_2$)

5,6,11,12-Tetrahydro-2,3,8,9-tetramethoxy-5-methyl-5,11-methanodibenz[b,f]azocinium perchlorate (221)

2-Methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (220, 2 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (200 cm^3) and stirred over anhydrous sodium

carbonate (0.5 g). The solution was electrolysed at a potential of + 0.8 volts until the current dropped below 10 mA. The anolyte was filtered and partially evaporated under reduced pressure. The residue was treated with water (400 cm^3) and extracted with dichloromethane (3 x 200 cm^3). The combined organic phases were washed with water (200 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a black solid which was added to acetone (50 cm^3). The insoluble material was collected by filtration and recrystallised from a large volume of methanol as white needles (0.28 g, 11%) m.p. 219°.

$\bar{\nu}$ max (cm^{-1}) : 1080 (C1-O)

λ max (nm (log ε)) : 2.11 (4.54), 231 (4.03), 290 (3.70)

δ (ppm, DMSO) : 3.18 (2H, d, $C_3\underline{H}_2$, $\underline{J}$ = $4H_z$), 3.37 (2H, d, $C\underline{H}_2$, $\underline{J}$ = $2H_z$), 3.6 - 3.9 (15H, 5 x 5, 4 x $OC\underline{H}_3$, $NC\underline{H}_3$), 4.08 (1H, complex, $C_4\underline{H}$), 4.76 (1H, d, C_1H, $\underline{J}$ = $14H_z$), 5.02 (1H, d, $C_1\underline{H}$, $\underline{J}$ = $14H_z$), 6.58 (1H, s), 6.72 (1H,s), 7.04 (1H, s), 7.48 (1H, s)

δ (ppm, DMSO) : 30.12 (q, $N\underline{C}H_3$), 35.48 (t, $\underline{C}_3H_2$), 48.54 (d, $\underline{C}_4H$), 55.53 (q, $O\underline{C}H_3$), 55.56 (q, $O\underline{C}H_3$), 55.64 (q, $O\underline{C}H_3$), 56.34 (q, $O\underline{C}H_3$), 61.92 (t, $\underline{C}H_2$), 68.04 (t, $\underline{C}_1H_2$), 104.56 (d), 109.00 (d), 111.65 (d), 112.09 (d), 119.07 (s), 122.22 (s), 126.33 (s), 133.05 (s), 148.38 (s), 148.42 (s), 149.09 (s), 149.79 (s)

$\underline{m/e}$: 355 (M-H), 341 ($M-CH_3$)

Found : C, 55.3; H, 5.7; N, 3.05; Cl, 7.9.

$C_{21}H_{26}NClO_8$ requires : C, 55.3; H, 5.7; N, 3.1; Cl, 7.8%

3,4-Dimethoxyacetophenone (222)

To an ice-cooled, stirred mixture of aluminium chloride (96.6 g, 0.72 mol) and a solution of veratrole (82.8 g, 76.4 cm^3, 0.6 mol) in dry benzene (400 cm^3) was added dropwise acetyl chloride (55 g, 49.8 cm^3, 0.7 mol). The mixture was stirred for 2 hours at room temperature and then poured onto ice (300 g). The layers were separated and the aqueous phase extracted with benzene (2 x 80 cm^3). The combined organic phases were washed with water (50 cm^3), 10% sodium hydroxide solution (2 x 50 cm^3) and water (50 cm^3), and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a colourless oil which was vacuum distilled. The product distilled (b.p. 135° at 0.4 mm Hg) as a colourless oil which solidified on standing (102 g, 94%) m.p. 49° (lit.[67] m.p. 49-50°).

$\bar{\nu}$ max (cm^{-1}) : 1665 (C=O)

λ max (nm (log ε)) : 208 (4.00), 232 (4.12), 278 (3.93), 310 (3.80)

δ (ppm, $CDCl_3$) : 2.57 (3H, s, $COC\underline{H}_3$), 3.95 (6H, s, 3 x $OC\underline{H}_3$), 6.88 (1H, d, $C_5\underline{H}$, $\underline{J}$ = 8H_z), 7.52 (1H, d, $C_2\underline{H}$, $\underline{J}$ = 2H_z), 7.55 (1H, dd, $C_6\underline{H}$, $\underline{J}_{26}$ = 2H_z), 7.55 (1H, dd, $C_6\underline{H}$, $\underline{J}_{26}$ = 2H_z, $\underline{J}_{56}$ = 8H_z)

$\underline{m/e}$: 180 ($M^{+\cdot}$), 165 (M-CH_3), 137 (M-$COCH_3$)

Metastables M* at 151.3 (180 → 165) and 113.7 (165 → 137)

3,4-Dimethoxybromoacetophenone (224)

(a) Bromine (20.9 g, 6.75 cm^3, 0.13 mol) in chloroform (40 cm^3) was added dropwise to a solution of 3,4-dimethoxyacetophenone (222, 22.5 g, 0.125 mol) in chloroform (300 cm^3) over a period of 1 hour at room temperature. The mixture was stirred for a further 0.5 hours and then washed with 2N sodium carbonate solution (2 x 125 cm^3) and water

(2 x 125 cm^3), and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a thick red gum.

m/e : 260/258, 180

(b) The above reaction was repeated but after stirring for only 10 minutes the orange crystalline precipitate of 3,4-dimethoxy-dibromoaceto phenone (223) was collected by filtration and washed with chloroform.

m/e : 340/338/336 ($M^{+\cdot}$), 179 ($M-Br_2$), 165 (ArCO), 137 (Ar), 82/80 (HBr)

The compound decomposed rapidly on exposure to moisture in the air evolving hydrogen bromide and leaving a black oil.

(c) To an ice-cooled, stirred solution of 3,4-dimethoxyaceto-phenone (222, 9 g, 0.05 mol) in a mixture of ether (250 cm^3) and chloroform (100 cm^3) was added dropwise a solution of bromine (8 g, 2.6 cm^3, 0.05 mol) in chloroform (50 cm^3) over a period of 1.5 hours. The mixture was stirred for a further 1 hour and then washed successively with water (50 cm^3), 5% sodium hydroxide solution (10 cm^3) and water (20 cm^3). The organic phase was dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a white solid which was recrystallised from 40% ethyl acetate in petroleum ether as colour-less plates (11.7 g, 91%) m.p. 79° (lit.[67] m.p. 80-81°).

$\bar{\nu}$ max (cm^{-1}) : 1680 (C=O)

λ max (nm (log ε)) : 206 (4.09), 234 (4.06), 287 (3.85), 318 (3.86)

δ (ppm, $CDCl_3$) : 3.95 (3H, s, $OC\underline{H}_3$), 3.97 (6H, s, $OC\underline{H}_3$), 4.42 (2H, s, $C\underline{H}_2$), 6.92 (1H, d, $C_5\underline{H}$, $\underline{J}$ = 8Hz), 7.54 (1H, d, $C_2\underline{H}$, $\underline{J}$ = 2Hz), 7.60 (1H, dd, $C_6\underline{H}$, $\underline{J}_{26}$ = 2Hz, $\underline{J}_{56}$ = 8Hz)

m/e : 260/258 ($M^{+\cdot}$), 165 (ArCO)

3,4-Dimethoxyphenylglyoxal ethyl hemiacetal (226)

A solution of 3,4-dimethoxybromoacetophenone (224, 14 g, 0.054 mol) and N,N-diethylhydroxylamine (5.13 g, 5.9 cm^3, 0.058 mol) in methanol (150 cm^3) was heated under reflux for 2.5 hours. The solvent was removed under reduced pressure and the residue stirred with ether (200 cm^3). The precipitated diethylamine hydrobromide was removed by filtration. The filtrate was evaporated under reduced pressure to leave a red oil to which was added ethanol (5 cm^3). The solution was stored at 0° for 24 hours. The bright yellow crystalline solid was collected by filtration and dried *in vacuo* at 50° for 4 hours (8.38 g, 65%) m.p. 91°.

$\bar{\nu}$ max (cm^{-1}) : 3300 (O-H), 1675 (C=O)

λ max (nm (log ε)) : 208 (4.00), 233 (4.09), 283 (3.94), 314 (3.84)

δ (ppm, $CDCl_3$) : 1.27 (3H, t, $C\underline{H}_3$, $\underline{J}$ = $7H_2$), 3.85 (2H, q, $C\underline{H}_2$, $\underline{J}$ = $7H_2$), 3.95 (3H, s, $OC\underline{H}_3$), 3.98 (3H, s, $OC\underline{H}_3$), 4.3 (1H, broad s, O$\underline{H}$, removed by deuteration), 5.68 (1H, s1 C$\underline{H}$), 6.95 (1H, d, $C_5\underline{H}$, $\underline{J}$ = $9H_2$), 7.61 (1H, d, $C_2\underline{H}$, $\underline{J}$ = $2H_2$), 7.70 (1H, dd, $C_6\underline{H}$, $\underline{J}_{26}$ = $2H_2$, $\underline{J}$ = $9H_2$)

$\underline{m/e}$: 240 (M^+), 194 (M-EtOH), 165 (ArCO), 137 (Ar), 46 (EtOH)

4-(3,4-Dimethoxyphenacyl)-6,7-dimethoxyisoquinoline hydrochloride (227)

A solution of 3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (201, 5.1 g, 0.02 mol) in concentrated hydrochloric acid (50 cm^3) was warmed to 80° and molten 3,4-dimethoxyphenylglyoxal ethyl hemiacetal (226, 9.6 g, 0.04 mol) was added together with hot ethanol (20 cm^3). The mixture was maintained at 100° for 1 hour and then cooled and

stored at 0° for 3 days. The solid was collected by filtration, washed with ethanol and then recrystallised from ethanol as colourless plates (1.95 g, 24%) m.p. 222° (lit.[69] m.p. 224-225°)

$\bar{\nu}$ max (cm^{-1}) : 3400 (n-H), 1680 (C=O), 1595 (C=N)

λ max (nm (log ε)) : 207 (4.24), 239 (4.64), 280 (4.08), 316 (4.03)

δ (ppm, CF_3COOD) : 4.08 (3H, s, $OC\underline{H}_3$), 4.13 (6H, s, 2 x $OC\underline{H}_3$), 4.24 (3H, s, $OC\underline{H}_3$), 5.12 (2H, s, $C\underline{H}_2$), 7.26 (1H, d, $C_5{}'\underline{H}$, $\underline{J}$ = $8H_z$), 7.45 (1H, s, $C_8\underline{H}$), 7.80 (1H, s, $C_5\underline{H}$), 7.83 (1H, d, $C_2{}'\underline{H}$, $\underline{J}$ = $2H_z$), 8.15 (1H, dd, $C_6{}'\underline{H}$, $\underline{J}_{2'6'}$ = $2H_z$, $\underline{J}_{5'6'}$ = $8H_z$), 8.40 (1H, d, $C_3\underline{H}$, $\underline{J}$ = $7H_z$), 9.28 (1H, d, $C_1\underline{H}$, $\underline{J}$ = $7H_z$)

$\underline{m/e}$: 367 (M-HCl), 202 (M-HCl-ArCO), 165 (ArCO), 137 (Ar)

Metastables M^* at 113.8 (165 → 137), 74.8 (367 → 165)

4-(2-Hydroxy-2- 3,4-dimethoxyphenyl ethyl)-6,7-dimethoxyisoquinoline (228)

4-(3,4-Dimethoxyphenacyl)-6,7-dimethoxyisoquinoline hydrochloride (227, 4 g, 0.01 mol) was suspended in ethanol (400 cm^3) and treated with sodium borohydride (4 g, 0.1 mol). The mixture was heated under reflux for 1 hour and then stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the residue dissolved in water (400 cm^3) and extracted with chloroform (3 x 400 cm^3). The combined organic phases were washed with water (400 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a colourless oil which was boiled with ethanol (5 cm^3). On cooling the white needles were collected by filtration (3.41 g, 92%) m.p. 77° (lit.[69] m.p. 75-80°).

$\bar{\nu}$ max (cm^{-1}) : 3225 (O-H), 1625 (C=N)

λ max (nm (log ε)) : 207 (4.48), 242 (4.63), 286 (3.69), 317 (3.39), 332 (3.39)

δ (ppm, DMSO) : 3.28 (2H, d, $C\underline{H}_2CH$, $\underline{J}$ = $6H_z$), 3.66 (3H, s, $OC\underline{H}_3$), 3.72 (3H, s, $OC\underline{H}_3$), 3.94 (6H, s, 2 x $OC\underline{H}_3$), 4.87 (1H, complex, $CH_2C\underline{H}OH$, collapses to t, $\underline{J}$ = $6H_z$, on deuteration), 5.35 (1H, d, $CHO\underline{H}$, $\underline{J}$ = $5H_z$, removed by deuteration), 6.8-6.9 (3H, complex aromatics), 7.23 (1H, s, $C_8\underline{H}$), 7.47 (1H, s, $C_5\underline{H}$), 8.09 (1H, s, $C_3\underline{H}$), 8.90 (1H, s, $C_1\underline{H}$)

$\underline{m/e}$: 369 (M^+), 351 ($M-H_2O$), 203 (dimethoxyisoquinoline), 167 (ArCHOH), 18 (H_2O)

4-(3,4-Dimethoxystyryl)-6,7-dimethoxyisoquinoline hydrochloride (229)

4-(2-Hydroxy-2-[3,4-dimethoxyphenyl]ethyl)-6,7-dimethoxyisoquinoline (228, 3.69 g, 0.01 mol) was dissolved in chloroform (750 cm^3) and saturated with hydrogen chloride over a period of 3 hours. Removal of the solvent under reduced pressure gave a solid which was recrystallised from ethanol as bright yellow needles (3.58 g, 92%) m.p. 219° (lit.[69] m.p. 213-215°).

$\bar{\nu}$ max (cm^{-1}) : 3400 (N-H), 1620 (C=N)

λ max (nm (log ε)) : 216 (4.35), 228 (4.37), 257 (4.36), 349 (4.11)

δ (ppm, $CDCl_3$) : 3.97 (3H, s, $OC\underline{H}_3$), 4.02 (3H, s, $OC\underline{H}_3$), 4.16 (3H, s, $OC\underline{H}_3$), 4.22 (3H, s, $OC\underline{H}_3$), 6.9 - 7.6 (7H, complex, aromatics and $C\underline{H}=C\underline{H}$), 7.76 (1H, s, $N\underline{H}$, removed by deuteration), 8.51 (1H, s, $C_3\underline{H}$), 9.35 (1H, s, $C_1\underline{H}$)

$^{m}/e$: 351 (M-HCl)

4-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyisoquinoline hydrochloride (230)

4-(3,4-Dimethoxystyryl)-6,7-dimethoxyisoquinoline hydrochloride (229, 1 g, 2.6 mmol) was dissolved in methanol (200 cm^3) and hydrogenated (4 atm) for 20 hours with platinum oxide (0.2 g) as catalyst. Filtration and removal of the solvent under reduced pressure gave a solid which was recrystallised from ethyl acetate as fine white needles (0.92 g, 90%) m.p. 158°.

$\bar{\nu}$ max (cm^{-1}) : 3400 (N-H), 1620 (C=N)

λ max (nm (log ε)) : 206 (4.52), 242 (4.67), 285 (3.87), 317 (3.62), 330 (3.56)

δ (ppm, DMSO) : 2.58 (1H, s, NH, removed by deuteration), 2.8 - 3.2 (2H, complex, CH_2CH_2), 3.3 - 3.6 (2H, complex, CH_2CH_2), 3.74 (6H, s, 2 x OCH_3), 4.01 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 6.6 - 7.0 (3H, complex, aromatics). 7.48 (1H, s, C_8H), 7.98 (1H, s, C_5H), 8.35 (1H, s, C_3H), 9.42 (1H, s, C_1H)

$^{m}/e$: 353 (M-HCl), 202 (M-$ArCH_2$), 151 ($ArCH_2$), 38/36 (HCl)

4-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyisoquinoline (231)

The hydrochloride salt (230, 3.9 g, 0.01 mol) was basefied with 2N ammonium hydroxide solution (250 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (50 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a gum which solidified on

trituration with ether. The solid was collected by filtration and recrystallised from 40% ethyl acetate in petroleum ether as white needles (3.46 g, 98%) m.p. 115° (lit.[71] m.p. 118-120°).

$\bar{\nu}$ max (cm^{-1}) : 1620 (C=N)

λ max (nm (log ε)) : 206 (4.57), 241 (4.80), 285 (3.98), 316 (3.64), 3.31 (3.57)

δ (ppm, DMSO) : 2.8 - 3.0 (2H, complex, $C\underline{H}_2CH_2$), 3.1 - 3.3 (2H, complex, $CH_2C\underline{H}_2$), 3.70 (6H, s, 2 x $OC\underline{H}_3$), 3.91 (3H, s, $OC\underline{H}_3$), 3.94 (3H, s, $OC\underline{H}_3$), 6.6 - 6.9 (3H, complex, aromatics), 7.22 (1H, s, $C_8\underline{H}$), 7.44 (1H, s, $C_5\underline{H}$), 8.17 (1H, s, $C_3\underline{H}$), 8.93 (1H, s, $C_1\underline{H}$)

m/e : 353 (M^+), 338 (M-CH_3), 202 (M-$ArCH_2$), 151 ($ArCH_2$)

4-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-2-methyl isoquinolinium iodide (232)

4-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyisoquinoline (231, 1.41 g, 4 mmol) was dissolved in warm acetone (15 cm^3) and treated with iodomethane (3 cm^3). The mixture was allowed to stand at room temperature for 1 hour and then the solid was collected and recrystallised from ethanol as pale yellow needles (1.88 g, 95%) m.p. 218° (lit.[71] m.p. 220-222°).

$\bar{\nu}$ max (cm^{-1}) : 1640 (C=N)

λ max (nm (log ε)) : 207 (4.54), 224 (4.43), 260 (4.64), 285 (2.63), 322 (3.33)

δ (ppm, DMSO) : 3.0 - 3.2 (2H, complex, $C\underline{H}_2CH_2$), 3.4 - 3.6 (2H, complex, $CH_2C\underline{H}_2$), 3.77 (6H, s, 2 x $OC\underline{H}_3$), 4.06 (3H, s, $OC\underline{H}_3$), 4.13 (3H, s, $OC\underline{H}_3$), 4.44 (3H, s, $NC\underline{H}_3$), 6.8 - 7.0 (3H, complex, aromatics), 7.48

(1H, s, $C_8\underline{H}$), 7.84 (1H, s, $C_5\underline{H}$), 8.49 (1H, s, $C_3\underline{H}$), 9.49 (1H, s, $C_1\underline{H}$)

$^m/_e$: 353 ($M-CH_3I$), 202 ($M-CH_3I-ArCH_2$), 151 ($ArCH_2$), 142 (CH_3I) 127 (I)

2-Methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (233)

The methiodide salt (232, 1 g, 2 mmol) was suspended in ethanol (200 cm^3) and water (10 cm^3), and treated with sodium borohydride (2 g). The mixture was heated under reflux for 1 hour and then stirred at room temperature for 20 hours. The solvent was removed under reduced pressure and the residue dissolved in water (300 cm^3) and extracted with ether (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a colourless gum (0.69 g, 93%).

$\bar{\nu}$ max (cm^{-1}) : 1135 (aromatic ether)

λ max (nm (log ε)) : 210 (4.56), 231 (4.22), 285 (3.76), 289 (3.76)

δ (ppm, $CDCl_3$) : 1.9 - 2.2 (2H, complex, $CH\underline{CH_2}CH_2$), 2.45 (3H, s, $NC\underline{H_3}$), 2.6 - 3.0 (5H, complex, $C\underline{H_2}C\underline{H}C\underline{H_2}C\underline{H_2}$), 3.38 (1H, d, $C_1\underline{H}$, $\underline{J}$ = 16H_z), 3.64 (1H, d, $C_1\underline{H}$, $\underline{J}$ = 16H_z), 3.86 (6H, s, 2 x $OC\underline{H_3}$), 3.88 (3H, s, $OC\underline{H_3}$), 3.90 (3H, s, $OC\underline{H_3}$), 6.56 (1H, s, $C_8\underline{H}$), 6.68 (1H, s, $C_5\underline{H}$), 6.7 - 6.8 (3H, complex, aromatics)

$^m/_e$: 371 ($M^{+\cdot}$), 356 ($M-CH_3$), 207 ($M-ArCH_2CH_2$), 192 ($M-ArCH_2CH_2-CH_3$), 151 ($ArCH_2$), 28 (HCNH)

Metastable M^* at 178.1 (207 → 192) and 115.5 (371 → 207)

Anodic oxidation of 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (233)

(a) The substrate (0.95 g) was dissolved in 0.1 M sodium perchlorate in dry acetonitrile (250 cm^3) and stirred with anhydrous sodium carbonate. The solution was electrolysed at a potential of 1.2 volts until the current dropped to 10 mA; 4.1 $F.mol^{-1}$ of charge was consumed. The anolyte was partially evaporated under reduced pressure and then treated with water (300 cm^3) and extracted with dichloromethane (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave an intractable brown tar.

(b) The above electrolysis was repeated at a potential of + 0.8 volts and 1.7 $F.mol^{-1}$ of charge was consumed. Work-up again gave a brown tar.

1,2,3,4-Tetrahydro-8,9,11,12-tetramethoxy-2-methyl-benzo[6,7]cyclohept[1,2,3-de]isoquinoline (234)

A solution of thallium (III) trifluoroacetate (0.75 g, 1.4 mmol) in dry acetonitrile (100 cm^3) and carbon tetrachloride (100 cm^3) was cooled to -40° under nitrogen in the absence of light. To this was added a solution of 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (233, 0.47 g, 1.27 mmol) in dry acetonitrile (15 cm^3) followed by boron trifluoride etherate (5 cm^3). The mixture was allowed to warm to room temperature and then stirred for 2 hours. The solvent was partially evaporated under reduced pressure and the residue treated with 2N ammonium hydroxide solution and extracted with chloroform (3 x 100 cm^3). The combined organic phases were washed with water (100 cm^3) and dried over anhydrous sodium

sulphate. Removal of the solvent under reduced pressure gave a brown oil which was subjected to column chromatography on basic alumina eluting with ether. Evaporation of the eluate under reduced pressure afforded a colourless gum which crystallised in the form of white rods on trituration with ether (0.2 g, 43%) m.p. 109°.

$\bar{\nu}$ max (cm^{-1}) : 1115 (aromatic ether)

λ max (nm ($\log \varepsilon$)) : 220 (4.58), 270 (4.06), 293 (3.95)

δ (ppm, DMSO) : 2.1-2.3 (5H, complex, $C\underline{H}_2C\underline{H}C\underline{H}_2$), 2.34 (3H, s, $NC\underline{H}_3$), 2.52 (2H, t, $C\underline{H}_2CH_2CH$, $\underline{J}$ = 12H_z), 3.10 (1H, d, $C_1\underline{H}$, $\underline{J}$ = 14H_z), 3.51 (3H, s, $OC\underline{H}_3$), 3.77 (3H, s, $OC\underline{H}_3$), 3.80 (1H, d, $C_1\underline{H}$, $\underline{J}$ = 14H_z), 3.84 (6H, s, 2 x $OC\underline{H}_3$), 6.76 (1H, s), 6.88 (1H, s), 6.99 (1H, s)

δ (ppm, DMSO) : 30.39 (t), 34.18 (d, $\underline{C}_4H$), 38.73 (t), 45.88 (q), 55.58 (q), 55.69 (q), 55.76 (q), 57.48 (t), 57.97 (t), 59.75 (q), 109.54 (d), 112.03 (d), 114.58 (d), 127.09 (s), 127.20 (s), 129.75 (s), 132.29 (s), 132.57 (s), 143.78 (s), 146.59 (s), 148.11 (s), 151.04 (s)

$^m/_e$: 369 ($M^{+\cdot}$), 368 (M-H)

Found : C, 71.4; H, 7.35; N, 3.85.

$C_{22}H_{27}NO_4$ requires : C, 71.5; H, 7.3; N, 3.8%

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